

eSupplement 1 – Protocol and Statistical Analysis Plan

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ICARE PROTOCOL: SUMMARY OF CHANGES

The ICARE protocol was updated 3 times post-proposal. This includes 2 updates after enrollment was initiated on 06/23/2009.

Pre-enrollment Revision #1 (eff. 03/06/2009, randomized accrual = 0): The first update was made 03/06/2009, prior to enrollment. A table detailing those revisions may be found on page 145 of this file. The revision updated key personnel, and recorded changes to secondary outcomes, eligibility criteria and screening processes.

Post-enrollment Revision #2 (eff. 04/10/10, randomized accrual = 68): The second revision was made 04/10/10. Eligibility criteria were broadened, including but not limited to: an extension in the eligibility window from 14 to 106 days post-stroke (originally 30 to 90 days), inclusion of recruitment sources in addition to inpatient rehabilitation, and permission of up to 6 hours (versus 2 hours) of outpatient OT prior to randomization. These changes were made in response to the observation of a changed healthcare landscape with reduced inpatient rehabilitation stays since the development of the proposal. This revision also included the addition of a brief medical examination within 72 hours of randomization as a safety check to support safe participation in the baseline evaluation; it was added proactively, not in response to an adverse event. Clarifications were made to the intervention parameters. The post-intervention evaluation window was specified as 16-20 weeks post-randomization in order to differentiate it from the 6-month evaluation period at 24-28 weeks. Information acquired in monthly monitoring phone calls was specified and changes in personnel were updated.

Post-enrollment Revision #3 (eff. 09/23/11, randomized accrual = 228): The third revision was made 09/23/11 and enabled enrollment of Spanish-language participants at one site (Rancho Los Amigos National Rehabilitation Center) after completion of a rigorous program to test the equivalency of all translated participant-interactive study materials.

ICARE STATISTICAL ANALYSIS PLAN: SUMMARY OF CHANGES

The original ICARE Statistical Analysis Plan (SAP) was followed with respect to descriptive statistics, univariate analyses (including distributional checks), handling of missing data and imputation, comparison of randomization across stratum, missing values, and patient characteristics. Some slight deviations were made from the original SAP in the final report to the ICARE DSMB. These deviations were detailed in the final report to the DSMB. They are: 1. Specification of how to proceed if there was not the possibility of 25 points increase of SIS hand function (e.g. baseline measure was less than 25 points from the maximum); 2. Results were presented as M+SD versus M+95% CI, and 3. There was an expansion of exploratory analyses. These are not presented in this paper.

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PRÉCIS

Study Title

Interdisciplinary Comprehensive Arm Rehab Evaluation (I-CARE) Stroke Initiative

Objectives

Our proposed objective is to randomize 360 participants into a phase III, multi-center (7 sites), single-blind RCT and investigate the effectiveness of a focused, intense, evidence-based, upper extremity rehabilitation program (Accelerated Skill Acquisition Program, ASAP), administered during the early post-acute outpatient interval, and to compare the effects of ASAP to that of an equivalent dose of usual and customary outpatient therapy (dose equivalent usual and customary care, DEUCC) on upper extremity functional recovery 1 year later. Our ultimate goal is to provide evidence to optimize post-stroke rehabilitation practice for those with mild to moderate upper limb impairments and reduce disability in the broadest sense.

Design and Outcomes

The I-CARE Stroke Initiative is a 5-year, phase III, single-blind, multi-center (7 clinical sites) RCT to compare Accelerated Skill Acquisition Program (ASAP), to a dose-equivalent (DEUCC) control group and an observational (monitoring only) control group (usual and customary care, UCC). We will recruit 360 adults, within one to three months of stroke onset, with mild to moderate upper extremity impairment.

Our primary outcome is the Wolf Motor Function Test (WMFT, time component). The Wolf Motor Function Test (WMFT)¹ determines the time required for patients with stroke to perform 15 everyday tasks with each upper extremity. Over the past 6 years, this measure has been used as either a primary or secondary outcome in at least 55 published studies. Tasks are sequenced so that the first seven tasks involve simple limb movements, primarily of the proximal musculature; the next ten tasks require manipulation and distal control. Each WMFT task is defined by a specific, detailed "anchoring" definition. For each task, information regarding patient positioning, placement of objects to be targeted or manipulated, distance of the participant to the object, whether seated or standing, and verbal instructions have all been operationalized.

Secondary outcome measures are listed here for completeness under the International Classification of Function and Disability Framework.

Body Structure/ Body Function: Arm Muscle Torque, WMFT (strength items), UE Fugl-Meyer (Motor), Depression (9-item self-report Patient Health Questionnaire-9), and 20-item Confidence in Arm and Hand Movements (CAHM).

Activity: Stroke Impact Scale (SIS), WMFT (functional ability scale), Action Research Arm Test (ARA), TEMPA, and Motor Activity Log-MAL-28 (QOM).

Participation: Reintegration to Normal Living Index (RNLI), Satisfaction with Life Scale (SWLS), Single Item Subjective Quality of Life (SQOL), and Exit Interview.

Comprehensive Body Structure/Function, Activity and Participation: Complete Stroke Impact Scale (SIS).

Non-Outcome Monitoring: Physiologic measures, Physical exam, and Immediate Post Intervention Interview.

Interventions and Duration

Accelerated Skill Acquisition Program (ASAP) Intervention: The ASAP program begins with an orientation session. Training sessions are 3x per week for 10 weeks for a total of 30 hours, with rest breaks as needed, but kept to a minimum. The training intervention is based on

the fundamental elements of skill acquisition through task-specific practice, impairment mitigation to increase capacity, and motivational enhancements to build self-confidence. Eight principles are used to guide ASAP intervention sessions: 1) Ensure challenging and meaningful practice, 2) address important mutable impairments, 3) enhance motor capacity through overload and specificity, 4) preserve natural goal-directedness in movement organization, 5) avoid artificial task breakdown when engaging in task-specific practice, 6) active patient involvement and opportunities for self-direction are feasible and desirable, 7) balance immediate and future needs for efficient motor skill and capacity enhancement with the development of confidence and self-management skills, and 8) drive task-specific self-confidence (self-efficacy) high through performance accomplishments.

Dose-Equivalent Usual and Customary Therapy (DEUCC) Intervention: Participants that are randomized to this group will be treated by a licensed and experienced occupational therapist working in the outpatient setting. The therapists are free to design and implement treatment according to their usual practice. We will require a minimal documentation burden from the therapist and project personal will monitor treatments throughout the 30 visits. The number of visits is constrained to 30 to comply with the ASAP therapy dose. The clinical site coordinator will inform the treating therapist of this stipulation only after the prescriptive dose has been determined and documented.

Usual and Customary Care Therapy (UCC) Intervention: Participants that are randomized to UCC will be treated by a licensed and experienced occupational therapist working in the outpatient setting. The therapists are free to design and implement treatment according to their usual practice. We will require a minimal documentation burden and monitor treatment throughout the UCC interval. This is an observation only group with no a priori stipulation of the number of visits. Documentation will be the same for UCC and DEUCC.

Duration: Time on study for all participants includes the intervention time (no greater than 10 weeks) and an additional 12 months post-intervention for follow-up. The schedule is as follows: pre-screen evaluation, study screen evaluation, baseline evaluation, randomization to group, intervention (10 weeks), post evaluation, 6 month post evaluation and 12 month post evaluation.

Sample Size and Population

We will recruit a total of 360 participants within one to three months post-stroke onset with mild to moderate upper extremity impairment. All persons that are admitted to the 7 rehabilitation sites will be screened for inclusion in the trial. All persons meeting eligibility criteria will be afforded the opportunity to participate in the trial. Women greater than or equal to 21 years of age and members of minority groups and their subpopulations will be included in this trial.

1 STUDY OBJECTIVES

1.1 PRIMARY OBJECTIVE

This RCT has one primary aim:

Specific Aim 1 (Primary): To compare the efficacy of a fully-defined, evidence-based and theoretically defensible therapy program (ASAP) and an equivalent dose of usual and customary occupational (*note from MAN: we should re-examine this as we are not persay comparing PT & OT*) therapy initiated within the earliest post-acute outpatient interval (1-3 months post stroke) for significant gains in the primary outcome of paretic upper extremity function 1 year after treatment.

Primary Hypothesis for SA 1: At 1 yr post treatment, the time score from the Wolf Motor Function Test (WMFT) will be significantly smaller (faster) after ASAP than usual and customary occupational (*note from MAN: we should re-examine this as we are not persay comparing PT & OT*) therapy care (DEUCC), controlled for dose.

Secondary Hypothesis for SA 1: At 1 yr post treatment, the proportion of patients with successful outcomes measured by the Stroke Impact Scale (SIS) hand domain and full SIS will be greater after ASAP than DEUCC, controlled for dose.

1.2 SECONDARY OBJECTIVES

Specific Aim 2A (Secondary): To compare the efficacy of a fully-defined, evidence-based and theoretically defensible therapy program (ASAP) to that of an observation only usual and customary (UCC) occupational (*note from MAN: we should re-examine this as we are not persay comparing PT & OT*) therapy program initiated within the earliest post-acute outpatient interval (1-3 months post stroke) for significant gains in the primary outcome of paretic upper extremity function 1-yr after treatment.

Hypothesis for SA 2: At 1 yr post treatment, the time score from the WMFT will be significantly smaller (faster) after ASAP than UCC, uncontrolled for dose.

Secondary Hypothesis for SA 2A: At 1 yr post treatment, the proportion of patients with successful outcomes measured by the SIS hand and full SIS will be greater after ASAP than UCC, uncontrolled for dose.

Specific Aim 2B: To compare the efficacy of one dose-equivalent usual and customary outpatient occupational (*note from MAN: if we change above, we should also change here*) therapy program (DEUCC) to an observation only, usual and customary outpatient occupational (*note from MAN: if we change above, we should also change here*) therapy (UCC) program initiated within the earliest post-acute outpatient interval (1-3 months post stroke) for significant gains in the primary outcome of paretic upper extremity function 1 yr after treatment.

Hypothesis for SA 2B: At 1 yr post treatment, the time score from the WMFT will be significantly smaller (faster) after DEUCC than UCC, uncontrolled for dose.

Secondary Hypothesis for SA 2B: At 1 yr post treatment, the proportion of patients with successful outcomes measured by the SIS hand domain and full SIS will be greater after DEUCC than for UCC, uncontrolled for dose.

This RCT will provide the critical foundation for at least three planned complementary studies designed to explore underlying mechanisms within subsets of the recruited

patient sample. These include, neuroimaging, biomechanics/neural control, and cost effectiveness studies currently under development.

2 BACKGROUND

2.1 RATIONALE

An assessment of current therapy practices during the post-acute period of outpatient rehabilitation and the state of phase II and III evidence has led to the development and re-design of this RCT proposal. Of the 700,000 individuals who experience a new or recurrent stroke each year, a majority have considerable residual disability²⁻⁷. Sixty-five percent of patients at 6 months are unable to incorporate the paretic hand effectively into daily activities^{5, 6}. In turn, this degree of functional deficit contributes to a reduced quality of life after stroke^{3, 6, 8, 9}. The extent of disability has been underplayed by the use of the Barthel Index¹⁰ that captures only basic activities of daily living such as self-care and does not extend to activities and participation at higher levels of functioning that are most affected by a residual upper extremity disability^{6, 11-14}. The past decade has witnessed an explosion of different therapy interventions designed to capitalize on the brain's inherent capability to rewire and learn well into old age and more importantly for rehabilitation, after injury. The most effective arm-focused interventions with the strongest evidence and potentially the most immediate and cost-effective appeal for the current health-care environment share a common emphasis on focused task-specific training applied with an intensity higher than usual care^{15, 16}. Therefore, our primary aim is to compare the efficacy of a fully defined, hybrid combination of the most effective interventions (forced-use/constraint-induced therapy and skill-based/impairment-mitigating motor learning training), the Accelerated Skill Acquisition Program (ASAP), to an equivalent dose of usual and customary outpatient therapy.

Although the exact proportion of stroke survivors who are mildly to moderately impaired is not known, conservative estimates range between 5% and 30%. These are individuals who return to the community but with significant disablement¹⁷. The paucity of dose-equivalent designs in the stroke upper extremity clinical trial literature and including our recent EXCITE trial¹⁸, highlights the necessity and importance of this phase III RCT evidence^{19, 20}. Unlike EXCITE, our intervention targets the immediate post-acute period, in large part because this timing is considered optimal for several important reasons: 1) it enables a supportive interaction between processes associated with experience-dependent and injury-induced cortical reorganization that are known to influence functional recovery^{21, 22}, 2) it may attenuate the detrimental effects of maladaptive compensatory strategies (e.g., learned non-use) currently promoted during inpatient rehabilitation⁵, that may with time be reinforced and become more difficult for the patient and clinician to reverse²³, 3) it is not too early as to be overly aggressive during a more vulnerable period both physiologically and psychologically^{21, 24}, and 4) it is simply not practical to introduce a distributed, 30-hr, upper extremity task-specific training program into an already dwindling acute inpatient length of stay^{5, 19}. Indeed, recently, Lang and colleagues showed that affected UE use is minimal during the inpatient rehab stay in patients with mild to moderate acute hemiparesis²⁵.

The following section describes the scientific and practical rationale for ASAP parameters including therapeutic dose and duration. Next, we describe the conceptual framework and how evidence from three domains of skill, capacity, and motivation integrate, inform and support the ASAP protocol. Finally, we describe the significance of this trial with respect to its potential impact on current practice for stroke rehabilitation.

2.1.1 Rationale For Parameters

An assessment of current therapy practices during the post-acute period of outpatient rehabilitation and the state of phase II and III evidence has led to the development and re-design of this RCT proposal. Of the 700,000 individuals who experience a new or recurrent stroke each year, a majority have considerable residual disability²⁻⁷. Sixty-five percent of patients at 6 months are unable to incorporate the paretic hand effectively into daily activities^{5, 6}. In turn, this degree of functional deficit contributes to a reduced quality of life after stroke^{3, 6, 8, 9}. The extent of disability has been underplayed by the use of the Barthel Index¹⁰ that captures only basic activities of daily living such as self-care and do not extend to activities and participation at higher levels of functioning that are most affected by a residual upper extremity disability^{6, 11-14}. The past decade has witnessed an explosion of different therapy interventions designed to capitalize on the brains inherent capability to rewire and learn well into old age and more importantly for rehabilitation, after injury. The most effective arm-focused interventions with the strongest evidence and potentially the most immediate and cost-effective appeal for the current health-care environment share a common emphasis on focused task-specific training applied with an intensity higher than usual care^{15, 16}. Therefore, our primary aim is to compare the efficacy of a fully defined, hybrid combination of the most effective interventions (forced-use/constraint-induced therapy and skill-based/impairment-mitigating motor learning training), the Accelerated Skill Acquisition Program (ASAP), to an equivalent dose of usual and customary outpatient therapy.

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Why apply the intervention one to three month post-stroke?

The recent ASA/AHS endorsed Clinical Practice Guidelines²⁶ review evidence for therapy intensity and duration. While the heterogeneity of the studies combined with borderline results in many trials limits the specificity and strength of any conclusions overall, the trials support the general concept that rehabilitation can improve functional outcomes, particularly in patients with lesser degrees of impairment. There is weak evidence for a dose-response relationship between intensity of the rehabilitation intervention and functional outcomes. For example Sterr and colleagues demonstrated that while both groups improved, 6 hrs of CIT led to greater improvements at 1 month on the WMFT and MAL than 3 hours delivered daily, over a two-week period in 15 adults with chronic hemiparesis²⁷. Despite limitations of these individual studies, the conclusions among several systematic reviews are fairly consistent: Two meta-analyses both concluded that greater intensity produces slightly better outcomes^{28, 29}. Kwakkel²⁹ reported a small but statistically significant intensity effect relationship in the rehabilitation of stroke patients. The literature specific to upper extremity treatment is mixed. Other than EXCITE, there are no multi-center trials in the literature. A recent two-center observer-blinded, stratified, block-randomized controlled trial with 91 patients (47 experimental, 44 control) within 1 yr of stroke who participated in three 90 min sessions/week for 6 weeks of task-oriented training for upper extremity did not improve voluntary movement or manual dexterity of the affected arm³⁰. These results were not surprising when considering the heterogeneous sample that was selected on walking impairment, and not arm impairment; in fact, 16% of the patients had no distal (wrist/fingers) movement capability. If no hand dexterity is apparent by 6 weeks after stroke the likelihood of achieving hand function at 6 months is poor³¹. This study highlights the need for well designed investigations with inclusion criteria that are matched to the specific intervention, in this case, that requires active motor participation.

What is a therapeutic dose of task-specific training: Why 30 hours for the therapy intervention?

For I-CARE, we chose a distributed schedule of 30 hrs of training for scientific and pragmatic reasons. We re-designed I-CARE to include a comparison control group, an observation only, usual and customary (UCC) outpatient occupational therapy. We expect considerable variation in the UCC dose both by site and across the 5-year monitoring period. These observation data will be important in the end from a policy standpoint and should be useful to estimate the cost if more prescriptive practice guidelines were to be implemented, especially if it can be shown to produce better outcomes. Pilot data from our multi-site outpatient survey suggests that 30 hrs distributed over 4-10 weeks would be somewhat higher than that commonly prescribed,

but still practical in that it would allow patients to participate in other concurrent therapy services (e.g., physical therapy and speech therapy). Thirty hours is 33% more than what we used in our single site phase II trial that commenced during inpatient and extending to outpatient (20 hrs distributed over 4-6 weeks)³²; it is 50% of that used for EXCITE (60 hrs over 2 weeks) during the 3-9 month post outpatient period³³; twice that used by Page³⁴ (15 hrs over 10 weeks, 30 min sessions, 3x/week) in a recent phase I acute trial of mCIT, and 55% of that prescribed in the recent home-based RCT of a multifaceted therapeutic exercise program (54 hrs over 12 weeks) in subacute stroke³⁵. *Therefore the 30 hr dose is well within the range of previous intervention trials shown to be effective, it is practical for the outpatient environment, yet it is likely higher than the usual average dose that is prescribed for this patient group.*

Why a 10 week duration?

This represents a departure from the ‘massed practice’ philosophy of the signature CIT protocol and the one we used in EXCITE, and in fact is closer to that prescribed in more recent reports that have used a modified CIT and distributed protocol of practice^{34, 36-43}. Together, there is considerable evidence for efficacy of task-specific practice using these more distributed training schedules in upper extremity Neurorehabilitation^{15, 44}. Although there are no direct comparisons (massed vs. distributed) in neurorehabilitation, there is a long history of this debate for motor learning⁴⁵. The term ‘massed’ practice is defined as a set of practice trials in which the performance-rest ratio is high and the proportion of rest between practice attempts is relatively shorter than the amount of time spent practicing. In contrast, ‘distributed’ practice refers to a set of practice trials in which the performance-rest ratio is low and the rest time between trials is longer than the amount of time spent practicing⁴⁶. Several reviews of the massed vs. distributed practice schedule for motor learning have concluded that the effects of the various performance and rest schedules seem to be different for discrete and continuous tasks. For discrete tasks, such as tossing a ball or fastening a button, reducing the rest time (i.e., massed practice) has little or no influence on learning, and in some cases less rest may even be beneficial. However, for continuous tasks, such as handwriting, fatigue-like states are more apt to build up within a performance bout, suggesting that massed practice would be undesirable. Therefore, the majority of laboratory findings would support this notion—less rest between performance epochs degrades performance and has an overall detrimental effect on learning⁴⁷. Finally, such a distributed schedule is attractive from a practical perspective both to the patient and clinic; clinics consider a therapy visit to be ~ 45 min to an hour and usual and customary OT for stroke ranges from 2-3x/week for up to 10 weeks. Therefore the DEUCC arm could be implemented 3x/wk (1 hr visit) over 10 weeks without major disruptions to the standard operating procedures of the majority of outpatient clinics. *Together, the evidence from recent mCIT studies, the scientific evidence from motor learning, and practical considerations, support the distributed schedule of task-specific training chosen for I-CARE.*

Why include mild to moderate stroke severity?

Collectively, these observations suggest that the highest potential to overcome upper extremity impairment and improve upper extremity function is seen among patients who

might be classified as “mild to moderately” impaired. These findings might apply to approximately 30%²³ of patients who have sustained a stroke and is supported by others^{31, 35}. Such considerations are important especially in harnessing functional potential during the first few months following stroke. In this context, it is prudent to recall that reduced lengths of stay and limited resources for subsequent subacute care have resulted in focused treatment toward compensatory behavior training, thus further limiting potentially beneficial voluntary activation of the impaired limb. This approach has become dictated by imposed constraints in treatment time and may be contributing to a learned non use. A recent evidence-based clinical practice case report for the *New England Journal of Medicine*, suggested that the strategies for therapy after hemiplegic stroke during weeks 2-6 of inpatient rehabilitation include “training in compensatory techniques” such as training in one-handed dressing, bathing, and using the toilet⁵. In summary, for I-CARE, we chose to target those patients with mild to moderate upper-extremity severity because this group is affected severely enough that they will not recover spontaneously, yet not so severely that they cannot participate in a systematic, focused and relatively intense and evidence-based task-specific training program. Our inclusion criteria are not as restrictive as those used in the EXCITE trial and therefore we expect to capture a larger percentage of those with upper-extremity impairments for I-CARE than we did for EXCITE.

There are no known potential risks of the interventions.

2.1.2 Significance Of This Study

Of the estimated persons with new stroke each year in the United States, 25-50% of stroke survivors experience persistent disability leading to partial or total dependence in activities of daily living. More effective treatment would lessen the disability, caregiver burden, and economic impact of stroke. Some prognostic figures suggest 65% of stroke survivors experience significant residual disability related to the upper extremity at 6 months⁶; the GAIN Americas trial estimated 38% had significant residual UE disability at 3 months. Using our EXCITE trial experience, we estimate that a total of 1689 of the 3404 screened EXCITE candidates, excluding those actually enrolled, would have met I-CARE inclusion criteria. By centering our protocol on the shared focus of CIT and ASAP in task-specific training, bringing forward unique evidence-based attributes of one (e.g., impairment mitigation, bilateral training, active patient problem-solving through motivational enhancements), and reconciling theoretically distinct features (e.g., forced versus informed patient choice in the use of the mitt) in this revised plan, we eliminate the unnecessary comparison between two overlapping approaches and directly ask a more significant question that has implications for the practice of stroke rehabilitation. Specifically, is an equivalent dose (30 hrs) of a fully developed and standardized application of ASAP better for long-term functional arm and hand use than that achieved with usual and customary care delivered over the same duration (10 weeks) and beginning within the post-acute (30-90 days) period? If our primary hypothesis is supported, the findings of I-CARE could change current practice patterns during post-acute outpatient therapy for those with mild to moderate baseline impairments; even if our primary hypothesis is not supported, our secondary aim to compare the effects of DEUCC to that of UCC has relevance for determining if dose

alone matters for functional outcomes. If our dose hypothesis is supported, the findings of I-CARE could establish recommendations for the number of outpatient visits necessary to achieve clinically meaningful outcomes and for which no guidelines currently exist. Further, current and future experimental interventions such as pharmacological agents, gene therapy, stem cell implants, and direct cortical stimulation inevitably will be combined with optimal standardized and effective neurorehabilitation protocols to organize neuroplastic effects and maximize benefits. Finally, the I-CARE initiative is aligned with the 2006 Report of the NINDS Stroke_Progress Review Group's established priorities for stroke recovery and rehabilitation research. Specifically, "to promote RCT's of important parameters of conventional rehabilitation interventions including: 1) Timing, dosing schedule...and 2) differential effects of various training paradigms.." ultimately to "develop science to maximize benefits of rehabilitation training and minimize adverse events".

2.2 SUPPORTING DATA

2.2.1 Study # 1: Extremity-Constraint Induced Therapy Evaluation, EXCITE (Wolf PI-HDR01 37606, EXCITE){Wolf, 2006 #3414}.

Context: Single site studies suggest that a 2-week program of Constraint Induced Movement therapy (CIMT) for patients more than 1 year after stroke and who maintain some hand and wrist movement can improve upper extremity function that persists for at least one year. **Objective:** To compare the effects of a multi-site, 2-week program of CIMT vs. usual and customary care on improvement in upper extremity function among patients 3-9 months post-stroke. **Design:** Prospective single-blind randomized multi-site clinical trial conducted at seven United States academic institutions between January 2001-03. **Participants:** 222 individuals with predominantly ischemic strokes.

Interventions: Participants were assigned to receive either CIMT (n = 106) (wearing a restraining mitt on the less affected hand while engaging in repetitive task practice and behavioral shaping with the hemiplegic hand) or usual and customary care n = 116) (ranging from no treatment after concluding formal rehabilitation to pharmacological or physiotherapeutic interventions) and were stratified by gender, pre-stroke dominant side, side of stroke, and level of paretic arm function. **Main Outcome Measures:** The Wolf Motor Function Test (WMFT), a measure of laboratory time and strength-based ability and quality of movement (functional ability), and the Motor Activity Log (MAL), a measure of how well and how often 30 common, daily activities are performed. **Results:** At 12 months, the CIMT group showed greater improvements than the control group on both the WMFT. Performance Time (19.3 s pre, 9.3 s 12 mo-52% reduction vs. 24.0 s pre, 17.7 s 12 mo-26% reduction in average time) between group difference, 34% 95% CI (12% - 51%), p < .001. and the MAL Amount of Use (1.21 pre, 2.13 12 mo vs. 1.15 pre, 1.65 12 mo) between group difference, 0.43 95% CI (.05 - .80), p < .001 and Quality of Movement (1.26 pre, 2.23 12 mo vs. 1.18 pre, 1.66 12 mo) between group difference, .48 95% CI (.13 - .84), p < .001. The CIMT group achieved a decrease of 19.5 in self-perceived hand function difficulty (SIS hand domain) vs. a decrease of 10.1 for the control group, between group difference, 9.42 (.27 - 18.57), p < .05.

Conclusions: Among patients who have sustained a stroke within the previous 3-9 months, CIMT produced statistically significant and clinically relevant improvements in arm motor function that persisted for at least one year and were not significantly

modified by age, gender, or initial level of paretic arm function. *These findings suggest that further research exploring central nervous system changes that accompany the observed motor gains and research on alternate models of CIMT delivery are warranted.* At present, 21 papers supported by the EXCITE grant have been published; 7 are in press, accepted for publication or in review; and an additional 23 are in various stages of preparation, including: 1) Persistence among improved outcome measures and 2): Impact of CI therapy: Comparison between 3-9 months or 1 year later. The content of papers in preparation is diverse including all aspects of the EXCITE Trial (methodological considerations, outcome papers, importance of intensity of training, health-related QOL, etc).

2.2.1.1 EXCITE Exit Interview

An Exit-Interview instrument was completed at the 24-month assessment (end of study) by a subset of 73 participants from 5 participating EXCITE sites. In addition to the 20-item self-efficacy measure, Confidence in Arm and Hand Movements (CAHM), the instrument addressed participants' perspectives on the CIT intervention and EXCITE study participation. Participants rated the helpfulness of the mitt worn during the intervention as a mean of 5.51 (SD = 1.62), on a 7 point scale in which 1 = not helpful at all and 7 = very helpful. Thirty percent of the respondents perceived the mitt as not helpful at all to somewhat helpful, while the remaining 70% felt the mitt was more than somewhat helpful to very helpful. Perceived helpfulness was moderately correlated with SIS hand function at 24 months, $r = .417$, $p < .0001$. Thirty-five subjects had their dominant hand affected. Of these, 37% reported regaining the use of their hand to write, while 20% reported regaining the use of their hand to carry a heavy object. Subjects who regained the use of their dominant hand for writing rated the helpfulness of the mitt significantly higher (mean = 6.15, SD = 1.28) than those who did not regain hand use for writing (mean = 5.00, SD = 1.80), $t(33) = 2.02$, $p = .051$. No differences in perceived mitt helpfulness were noted in those who did or did not regain heavy object carrying capacity. It can be noted that the battery of tasks used in CIT training tends to favor dexterity rather than strength, and certainly unimanual as opposed to bimanual tasks, given the extensive mitt use. In an open-ended format, exit interview respondents were asked to indicate activities that they had wanted to do before CIT intervention that they still could not do. In addition to tasks involving dexterity in the affected hand (e.g., picking up small objects, using tools, and writing), responses included tasks involving both hands acting interdependently (e.g., cutting and peeling vegetables, buttoning shirts, playing golf or musical instruments) as well as in parallel (e.g., holding a book, carrying large or heavy objects, carrying hot objects).

Relevant to I-CARE, these findings suggest that: 1) participants generally found the mitt helpful in encouraging affected hand use, though a minority did not, 2) there are a substantial number of bimanual tasks that these individuals would like to regain, and 3) consistent with a Rasch analysis of SIS hand function items³, tasks requiring muscle strength are particularly difficult for individuals after stroke⁴⁸. Finally, the EXCITE persistence analysis showed improved SIS domains at 16 and 24 months in the immediate group. *These findings support decisions about ASAP to: 1) encourage mitt use in collaborative planning, especially when tasks involve dexterity or fine motor*

control, 2) require that at least one preferred task involve bimanual activity, and 3) incorporate capacity building for strength-requiring tasks (e.g., lifting grocery bag), in addition to those that challenge fine motor control and dexterity.

2.2.2 Study # 2, Secondary Outcome Measure: SIS Hand Domain From EXCITE And Other Data Sets Closer To The I-CARE Post-Acute Period

Background: The SIS is a well-established health status measure with reliability and validity^{17, 49} and in each of the eight domains. Duncan and colleagues report that at baseline the SIS had acceptable reliability with alpha coefficients of .75-.87, except for strength with an internal consistency coefficient of .63⁵⁰. We chose the Hand Function portion of the full SIS for the secondary outcome for several reasons^{51, 52}: 1) it represents a valid and reliable outcome that is well aligned with I-CARE specific aims, 2) it can be easily interpreted for clinical meaningfulness, 3) we obtained SIS hand function data from the acute (VECTORS) and post-acute period (Kansas City study) where dynamic change is high and I-CARE intervention occurs, and 4) using EXCITE data, there was high correspondence between patient's perception of SIS hand function at two years post, and our laboratory-based primary outcome measure of hand and arm function, the WMFT log mean transformed time score ($r = -0.64$, $p < .0001$, $n = 124$), and other self-report measures including the Motor Activity Log-Amount of use ($r = .68$, $p < .0001$, $n = 124$), and Motor Activity Log-How Well ($r = .68$, $p < .0001$, $n = 124$). This provides evidence for construct validity for this self-report measure. **Clinical Meaningfulness:** The SIS was developed from focus groups of stroke survivors; the SIS hand function domain lists five activities of the hand that were most important for stroke patients to accomplish; the scale provides a metric of perceived difficulty in performing each of these tasks between 1 (could not do at all) and 5 (not difficult at all). The 5-point scale is normalized to 100% with each integer rating representing a 25-point increment on the normalized scale (e.g., difference between 1 and 2 is 25 points). Therefore, a 1 category shift in perceived difficulty would represent a 25-point change on the full normalized scale. A minimum of 25 point increase (less difficult) has face validity for a clinically meaningful change and one that can be compared across studies including EXCITE. **EXCITE and SIS:** One year outcome data from the EXCITE trial showed a significant change in self-reported hand function for the CIT compared to the control group. In addition, this improvement on the SIS hand function corresponded with a significant change in WMFT time scores that were significantly greater for the CIT compared to the control group at one year¹⁸. Using a 25 point change (one category), as a measure of successful outcome, we estimated the proportion of subjects in each group who achieved success. At one year, 24% of the control group and 49% of the CIT group (difference of 25%) met this criterion for success. **Acute Time Frame and SIS:** We compared estimates of success rate (i.e., 1 or more category change on SIS hand function) from three separate sample control groups including, EXCITE (subacute, non equivalent dose), VECTORS (acute, equivalent dose), and Kansas City (1-3 months, non equivalent dose) home-based exercise study³⁵, to more fully anticipate the impact of providing ASAP during a dynamic recovery period. As expected, the estimates of control group success rates from these samples were ordered from acute (46%, $n = 13$), post-acute (35%, $n = 71$), to subacute (24%, $n = 86$).

2.2.3 Study # 3: Stroke Arm Recovery In Acute/Post-Acute Stroke (Winstein PI-HD R03 36212, STAR)

Purpose: The Stroke Arm Recovery trial (STAR) was a single-center, non-blinded, phase II RCT (baseline, post-intervention, 9 mo) that evaluated the immediate and long-term effects of two upper-extremity rehabilitation approaches for stroke arm recovery compared with standard therapy in participants stratified by stroke severity in the acute inpatient rehabilitation setting. The study was conducted at Rancho Los Amigos National Rehabilitation Center, also a site for I-CARE. This trial was completed in 2003 with the primary outcomes published in 2004³². **Methods:** Subjects were recruited within 16 days of stroke from inpatient rehabilitation and randomized within severity strata (Orpington Prognostic Scale) into 1 of 3 intervention groups. In addition to standard therapy care (SC) participants were randomized into either functional task-specific practice (FT) or strength-based/impairment training (ST) groups, each of which received 20 additional hours of upper-extremity therapy beyond standard therapy distributed over a 4- to 6-week period across all three groups (i.e., therapy was added to the standard dose of occupational therapy). Because the average inpatient stay became less than 4 weeks (23.1 +/- 11.1d), during the study, the additional time needed to fulfill the 20 hours was completed in an outpatient setting; the same setting we propose for I-CARE. Performance measures of impairment (upper extremity Fugl-Meyer motor), strength (isometric torque), and function (Functional Test of the Hemiparetic Upper Extremity), were used. **Results:** Compared with standard care participants, those in the FT and ST groups had significantly greater increases in Fugl-Meyer motor scores ($p = .04$) and isometric torque ($p = .02$) post-treatment. Treatment benefit was primarily in the less severe participants (Orpington Score, ≤ 4.1), where improvement in FT and ST group Fugl-Meyer motor scores more than doubled that of the standard therapy group. Similar results were found for the FTHUE and isometric torque. At the 9 month follow-up, the less severe FT group continued to make gains in isometric muscle torque, significantly exceeding those of the ST group ($p < .05$). At 9 months and despite participant attrition in the less severe cohort, the FT group outperformed the ST group in improvement of upper-extremity isometric torque. In contrast, the performance of the ST group approached the level of the control group while the FT group accelerated its gain in isometric torque over the post-treatment to 9-month interval. This difference at follow-up suggests that therapy contents or its correlates—and not simply therapy dose—was critical to the treatment effect. Surprisingly, the FT group demonstrated better performance than the ST group on a strength measure. One explanation for this counterintuitive result may be that functional task-specific practice provided a more favorable and meaningful context for strength gains that were mediated through persistent daily arm and hand use than the resistance exercises, alone. There is evidence that intervention strategies that provide context-relevant, meaningful engagement in activities and promote self-management of that activity are more beneficial for skill acquisition and transfer than rote exercises or passive modalities⁵³⁻⁵⁶. *This study and its results factored heavily into the development of the I-CARE proposal and more specifically, the task-specific training/impairment mitigation protocol for ASAP.*

2.2.4 STUDY # 4: Very Early Constraint Induced Movement Therapy (VECTORS): Phase II Trial Results (Dromerick PI-NS R21 41261)

Overview: The VECTORS primary result was presented at the International Stroke Meeting in February 2007; manuscript preparation is underway. This trial of CI therapy begins within 14 days of stroke onset, demonstrating the experience of the research team in rehabilitation trials earlier than I-CARE or STAR. **Purpose:** VECTORS was a Phase II single center pilot randomized controlled clinical trial of the early application of Constraint Induced Movement Therapy (CIMT). Goals included estimation of effect size, selection of primary endpoints, and determination of safety issues (particularly activity-dependent lesion enlargement). **Methods:** Subjects were assigned using adaptive randomization into the control group (2 hours, traditional OT), a dose-matched CIT group (2 hours shaping, 6h/day constraint), or the high intensity CIT group (3 hours shaping, 90% waking hours constraint) at inpatient rehabilitation admission (**Table 2.2.4**). Inclusion criteria included ischemic or hemorrhagic stroke within 28 days of onset; no prior stroke-related neurologic impairment; need for inpatient rehabilitation; NIH Stroke Scale (NIHSS) aphasia, command, consciousness and sensory items < 1; NIHSS neglect = 0; and persistently hemiparetic UE with some residual voluntary movement. Blinded raters evaluated subjects at randomization, end of treatment (14d), and the primary endpoint (90d). The prespecified primary dependent measure was the total Action Research Arm Test (ARAT) at 90 days after randomization. Mixed model analyses were performed. A subsample (n=9) underwent MRI imaging (apparent diffusion coefficient [ADC] mapping) at study baseline and Day 7-9 to determine if new neuronal injury occurred during study treatment. **Results:** 52 participants (mean age 63.9 + 14 yr) were randomized 9.65 + 4.5 days after onset. Mean NIHSS was 5.3 + 1.8; mean Action Research Arm Test (ARA) score was 22.5 + 15.6; 77% had ischemic stroke. Groups were equivalent at baseline on all randomization variables. As expected, all groups improved with time on the total ARA score. There was a significant time x group interaction ($F = 3.1$ $p < .01$), such that the high intensity CIT group had significantly worse scores at Day 90. No significant differences were found between the dose-matched CIT and control groups at Day 90. Similar time x group interactions were observed using the Wolf Motor Function Test Functional Ability ($F = 3.3$, $p < .01$). No clinical safety issues were encountered; ADC maps revealed no evidence of new neuronal damage. **Conclusion:** Our results did not support the hypothesis that CIT therapy is superior to equal doses of conventional therapy in the acute inpatient rehabilitation setting. A dose response relationship was observed, where a higher dose of CIT was associated with less motor recovery. There was no evidence of activity-dependent lesion enlargement. *Our results highlight the need for clinical trial designs that directly and empirically determine the efficacy of specific treatments at specific delivery schedules during each phase of stroke care. I-CARE does exactly this.*

Table 2.2.4 STUDY # 4: Very Early Constraint Induced Movement Therapy (VECTORS): Phase II Trial Results (Dromerick PI-NS R21 41261)

Table 2.2.4	Total Sample	Control	Low CIMT	High CIMT
Age	63.9 \pm 14	64.7 \pm 14.6	62.8 \pm 12.8	64.5 \pm 15.5
Days since stroke	9.7 \pm 4.6	--	8.8 \pm 3.1	9.94 \pm 4.8
Total NIHSS	5.3 \pm 1.8	5.5 \pm 1.8	5.1 \pm 1.8	5.31 \pm 1.8
Total ARA, impaired	22.5 \pm 15.3	19.7 \pm 13.9	22.7 \pm 14.3	25.4 \pm 18.0
FIM Motor	57.8 \pm 11.1	56.7 \pm 12.2	57.1 \pm 9.5	59.8 \pm 12.1
% Female	60%	65%	68%	44%
Race				
African American	42%	47%	37%	44%
Caucasian	57%	53%	58%	56%
Stroke Lesion				
% Ischemic	77%	76%	74%	81%

2.2.5 Study #5: I-CARE Proof Of Principle

Purpose: The purpose of gathering these pilot data was to demonstrate proof of principle for the model of task-specific training that is ASAP: 1) verify our earlier findings that patients who were between 1-3 months could manage the ASAP intervention schedule, comply with the protocol and actively participate; 2) determine recruitment feasibility, enrollment and systematic application of ASAP across multiple sites; 4) successfully implement each of the three elements; 5) demonstrate that therapy applied post inpatient is naturally feasible and safe. There was no control group, evaluators were not blinded, and there was no follow-up; because demonstrating efficacy was not our purpose. **Methods:** Three centers (USC, Emory, NRH) submitted and obtained IRB approval to conduct the study and initially prospectively recruited 6 participants (2/center) within 3 months post CVA; NRH has recently recruited an additional participant whose data are included. Table 2.2.5.a shows data by participant and includes medications and comorbidities. Our sample included diversity in baseline characteristics, initial motor impairment, demographics, and comorbidities. On average per site, 32 participants were referred, 10 were screened, and 2 were enrolled, matching our overall 6% projected capture rate. Each participant received medical clearance and passed a screening evaluation to determine eligibility. The 30 hr dose was the same as our proposal, but we used a more compact distribution of 2 hr/d, 5 d/wk for 3 weeks. In each case, ASAP was administered one-on-one by a trained and standardized intervention therapist who had participated in a 3-day training workshop at USC in spring, 2005. We used the old ASAP protocol, which differed on one dimension from the revised protocol; we did not use a constraint device. Recruitment and training was accomplished but with nine protocol violations, all related to missed treatments that were rescheduled. This along with the other reasons described in Sec 2.1 (Rationale) provided the rationale for a more distributed schedule. We modified the duration to accommodate a more standard outpatient treatment schedule. We found the ASAP protocol to be replicated relatively smoothly across our sites, further supporting our proof of principle.

Table 2.2.5.b includes a Case Analysis (participant # 7) that maps specific tasks and training procedures to each of the three ASAP elements across three days of training.

Table 2.2.5.a Study # 5: I-CARE Multi-Center Proof of Principle (ASAP) Preliminary Data

Table 2.2.5.a Proof of Principle Preliminary Data							
	NRH			Emory		USC	
Subject	1	2	3	4	5	6	7
MEDICAL							
CVA Lesion Side (L/R)	R-CVA	R-CVA	R-CVA	L-CVA	L-CVA	L-CVA	R-CVA
Dominant Hand Most Affected	No	No	No	Yes	Yes	Yes	No
Co-morbidities/Past Medical History*	1 - 7	1, 8, 9	10 - 15	1, 12, 16	1	1	1
Medications**	1 - 14	NT	1, 9, 11, 12, 15 - 17	18, 19	1, 20	21	11, 18, 22, 23
DEMOGRAPHICS							
Race/Ethnicity	AtAm	AtAm	AtAm	AtAm	AtAm	Asian-Am	Caucasian
Age (years)	70	53	71	40	46	62	72
Gender	female	female	male	male	male	male	male
Marital Status (S-single, M-married)	S	S	NA	M	M	S	M
TIMING							
Length of Hospital Stay (days)	11	NA	26	30	28	28	NA
Screen (days since onset)	22	26	85	60	20	26	48
Baseline Eval (days since onset)	22	26	86	79	27	53	49
Post Eval (days since onset)	54	47	109	108	53	84	84
SCREEN							
Ospington Prognostic Scale	NT	NT	NT	0.4	1.2	2	0.8
NIHSS Total	2	6	N/T	2	4	2	2
MMSE	24	29	21	28	28	30	28
Barthel Index (prior to stroke)	95	75	95	100	100	100	100
EVALUATION							
Fugl-Meyer baseline	55	41	54	50	32	38	37
Fugl-Meyer post-intervention	55	41	54	57	53	42	58
WMFT-baseline (avg time in s)	6.20	9.77	6.04	2.56	44.40	28.21	5.75
WMFT-post (avg time in s)	3.57	2.20	2.79	1.60	2.90	63.38	4.59
SIS-Hand (sum)	NT	11	18	NT	NT	NT	NT
SIS Total (sum)	NT	147	242	NT	NT	NT	NT
Brief Self Efficacy (initial - final)	2-10	5-10	5-10	1-10	7-10	5-7	4-7
Baseline CAHM (average)	20	12.25	58.5	94.5	65.5	30	50
Post-Intervention CAHM (average)	95	NT	NT	100	99.25	57.5	52.6
PHQ 9 baseline	10	18	1	0	4	0	5
PHQ 9 post-intervention	NT	NT	2	NT	NT	0	7
NA = not available; NT = not tested							
* Co-morbidity/Past Medical History codes: 1 HTN, 2 COPD, 3 anemia, 4 sleep apnea, 5 atrial fibrillation, 6 R knee ligament repair, 7 hysterectomy, 8 DM, 9 hypercholestermia, 10 pacemaker/bradycardia, 11 seizure disorder, 12 hyperlipidemia, 13 thrombocytopenia, 14 R calf DVT, 15 mild R UE CRPS, 16 hypomagnesemia							
** Medication codes: 1 Coumadin, 2 Cardizem, 3 Prandin, 4 Saxside, 5 Potassium Chloride, 6 Foradil, 7 Flovent, 8 Fluticasone, 9 Pepcid, 10 Lisinopril, 11 Lipitor, 12 Sennas, 13 Lantus, 14 Tylenol, 15 Multivitamin, 16 Plavix, 17 Keppra, 18 Aspirin, 19 Zocor, 20 Norvasc, 21 Benazepril Study, 22 Divan, 23 Niaspin							

Table 2.2.5.b Study # 5: I-CARE Multi-Center Proof of Principle (ASAP) Case Analysis-Integration of ASAP Elements

Case Analysis-Integration of ASAP Elements – Participant #7

Element(s)	Description	Comments
Orientation Session		
MOTIVATION: Collaboration agreement	Participant oriented to ASAP purpose and principles, organization, action planning [optional mitt use]. Future sessions are scheduled.	
MOTIVATION: Task collaboration	S7 designated 4 specific tasks (including ones with bimanual, strength, dexterity requirements), including one as his priority task.	Priority task selected was use of his impaired arm and hand to eat, including management of utensils and mug. Other chosen tasks: card manipulation (shuffling, dealing, holding, placing), writing, handyman tool use (e.g., hammer).
Training Days		
	Assess vitals signs	Within normal limits (all days)
MOTIVATION: Brief Self-Efficacy assessment for priority task	S7 was asked how confident he was to be able to perform specific chosen task. Then asked to problem-solve by providing thoughts on what could be done to increase confidence in next week (S7 Day 1: "Exercise; what else is there?").	Brief self-efficacy assessments 4 times, including first and last sessions. Initial brief self-efficacy score = 4 for eating/management of utensils/mug. Later scores were 5 (middle session) and 7 (end of training).
MOTIVATION and SKILL: Action plans for self-management skills/extended practice	Set-up (end of sessions) and debriefing (beginning of sessions) of participant's action plans.	S7 reported on home tasks of writing and eating with impaired arm/hand (day 8), tasks of writing and lifting boxes in garage (day 15).

Element(s)	Description	Comments
Training Days		
SKILL: task-specific practice (priority task) and IMPAIRMENT MITIGATION: coordination, selective movement, precision; force modulation, and MOTIVATION: collaboration and challenge	Eating skills (use of knife for cutting, pouring liquid into varied size mugs/cups). Progressed from use of knife with built-up handle (Day 1); knife without build-up for cutting around targets in simulated food, drinking from mug filled with varied amounts of water in mug (Day 8); use of knife without built-up handle to cut muffin, break and peel an egg, placed various sized beans into varied size containers. Task practiced for 25-30 minutes in different participant-selected order each day.	S7 limited by decreased grip strength and fine motor control; reported 6 out of 5 difficulty with cutting and 3-4 out of 5 fork and spoon use (Day 1). S7 limited by decreased forearm pronation, shoulder abduction with internal rotation, selective use (coordination) of the arm and hand (Day 8). S7 directed practice session with ideas to increase the level of difficulty and challenge (Day 15).
SKILL: task-specific practice and IMPAIRMENT MITIGATION: speed, intersegmental coordination, selective finger movement, and MOTIVATION: collaboration and challenge	Card manipulation (shuffling, dealing, holding, placing). S7 challenged to speed up movements. Repetitions timed. Task practiced for 25-30 minutes in different order each day.	Day 1: S7 prompted to self-assess difficulty of task and begin problem solving with therapist to increase challenge, implemented 5-point difficulty rating scale. Day 8: S7 dealt cards farther away from midline and body, able to deal and pick-up card faster than previous day. Day 15: S7 chose to vary the type of hand technique to pick up cards, such as finger to thumb, to sliding card to edge of table; reports playing cards with friends.

Element(s)	Description	Comments
Training Days		
SKILL: task-specific practice and IMPAIRMENT MITIGATION: precision; force modulation; coordination; selective movement, and MOTIVATION: collaboration and challenge	Writing (use of pencil for printing and cursive writing). S7 progressed from use of a pencil with built-up handle and pencil manipulation on table top (Day 1), to copying a paragraph, writing in large and small print and cursively (Day 8), to writing without built-up handle, writing on triplicate form, drawing a picture (Day 15). Task practiced for 25-30 minutes in different order each day.	Day 1: S7 required 80.04 seconds to pick up pencil and print name; reported 3 out of 5 difficulty. S7 chose order of writing tasks; stated on day 6 "...writing is a little better...I can read it." S7 reported being pleased with his writing; chose to draw a picture; able to write 3/4 of a page in 10 minutes (Day 15).
SKILL: task-specific practice and IMPAIRMENT MITIGATION: precision; force modulation; load/intensity; endurance work to fatigue; coordination; selective movement, and MOTIVATION: collaboration and challenge	"Handyman" activities (hammering, taking measurements at varied angles, heights, surfaces with ruler and making measurements with pencil; sanding wood; pulling duct tape off a roll and placing on wall at varied heights, plugging cords in/removing from socket). Grip strength targeted. Task practiced for 25-30 minutes in different order each day.	Day 1: missed nail on 10 of 25 attempts; Days 8 and 15: S7 offered suggestions for activity progression based on level of difficulty (e.g., reach farther from body when taking measurements).
MOTIVATION: Task collaboration	Tasks chosen by S7 for next day	Order of tasks practice differed.
	Assess vital signs, pain, and fatigue	Vitals: within normal limits (all days); pain absent; fatigue 6 and 5 out of 10 on Days 8 and 15.
	Exit interview (Day 15)	S7 reported that he resumed playing cards with friends and playing games with grandchildren such as building houses out of cards, coloring, jigsaw puzzles; preparing to get his driver's license and is glad to have practiced writing his signature; reported being pleased with the program and expressed appreciation "... you have changed my life and I thank you."

2.2.6 Study # 6: Recruitment Feasibility

Between July and October, 2006, we conducted a feasibility study through systematic chart review of the last 100 stroke admits to each of our clinical sites. The purpose was to determine what percentage of patients would have met inclusion criteria and to determine if our planned recruitment rate was feasible. Because most centers do not routinely administer the NIHSS, Orpington Prognostic Scale, or Fugl-Meyer, we selected alternative measures of upper extremity motor, cognitive, sensory, and neglect that would approximate our criteria, yet be achievable from the chart review. The following criteria were used: 1) presence of distal upper extremity movement (wrist and/or fingers), 2) No severe neglect, 3) UE sensation intact to no more than mildly impaired, and 4) Adequate cognition determined by FIM comprehension and problem solving scores ≥ 4 . **Table 2.2.6** summarizes the results. We estimated of the number of eligible participants/mo by dividing the number eligible by the inclusive months of chart review. From past experience, we estimated that for various reasons, only 75% of those found eligible would be randomized. Our findings suggest there is high probability that each center (Washington DC, Georgia and California) can meet target recruitment goals (3 participants/mo). Additional demographic data (gender, race, age, d/c destination, outpatient occupational therapy referral) and FIM admission and discharge scores were collected.

Table 2.2.6 Study # 6: Recruitment Feasibility Study Results for Each Collaborating Center

Table 2.2.6 Recruitment feasibility study results for each collaborating center							
Centers	DC	GA	CA				
Sites	NRH	CRM	CFRMC	CSMC	HRMA	LBMC	RLA
Charts Reviewed	100	86	100	100	78	100	100
% Present Wrist/Finger Movement	93.0%	75.6%	68.0%	85.0%	80.8%	77.0%	65.0%
% Severe Neglect	2.0%	14.0%	25.0%	2.0%	12.8%	15.0%	15.0%
% Upper Extremity Sensation Intact or Mildly Impaired	74.0%	79.1%	37.0%	75.0%	85.9%	88.0%	50.0%
% FIM Comprehension ≥ 4	85.0%	72.1%	NA	85.0%	79.5%	76.0%	83.0%
% FIM Problem Solving ≥ 4	79.0%	70.9%	NA	61.0%	70.5%	57.0%	56.0%
% Meet Inclusion Criteria	39.0%	30.2%	32.0%	43.0%	28.2%	38.0%	29.0%
Review Period (mos)	6	9	9	6	20	13	6
Estimated # Eligible (patients/mo)	6.5	3.4	3.6	7.2	1.4	2.9	4.8
Estimated I-CARE Recruitment (patients/mo)	4.9	2.2	2.7	5.4	0.8	2.2	3.6
NRH - National Rehabilitation Hospital, Washington, DC;							
CRM - Center for Rehabilitation Medicine, Atlanta, GA;							
CFRMC – Centinela Freeman Regional Medical Center, Los Angeles, CA;							
CSMC - Cedars-Sinai Medical Center, Los Angeles, CA;							
HRMA - Huntington Rehabilitation Medicine Associates, Pasadena, CA;							
LBMC - Long Beach Memorial Medical Center, Long Beach, CA;							
RLA - Rancho Los Amigos National Rehabilitation Center, Downey, CA.							
FIM - Functional Independence Measure (functional item scores range from 1 Total Assistance to 7 Independent; note 4 = Minimum Assistance)							
Estimated I-CARE Recruitment - Based upon 75% capture rate							

3 STUDY DESIGN

3.1 RESEARCH DESIGN AND METHODS: OVERALL PLAN

The primary objective of the Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (I-CARE) trial is to conduct a phase III, single-blind, multi-center RCT to compare Accelerated Skill Acquisition Program (ASAP), to a dose-equivalent (DEUCC) control group (Specific Aim 1) and an observational (monitoring only) control group (Specific Aim 2). Our primary outcome is laboratory-based performance of the WMFT measured at 1 year after participation. ASAP includes 30 hours of one-on-one training delivered over 10 weeks. We will recruit 360 adults, within one to three months of stroke onset, with mild to moderate upper extremity impairment. Participants will be randomized to one of three treatment groups, and the primary dependent measure is change in WMFT time score at 1 year after intervention. Secondary outcome measures will be used to evaluate the impact of treatment interventions on self-perception of paretic hand function and full scale health status.

This is a multi-site (7 clinical sites), prospective randomized single-blind, clinical intervention trial with screening and enrollment between 5 – 75 days post stroke, (enrollment within post-stroke interval during in-patient rehabilitation, in most cases). Participants who are not eligible at the initial screen because they do not exhibit enough voluntary motion will be followed prospectively when possible to 30 days post stroke. After medical clearance, participants will be randomized to one of three groups. Please see Figure 3.1 for an overview of the study flow.

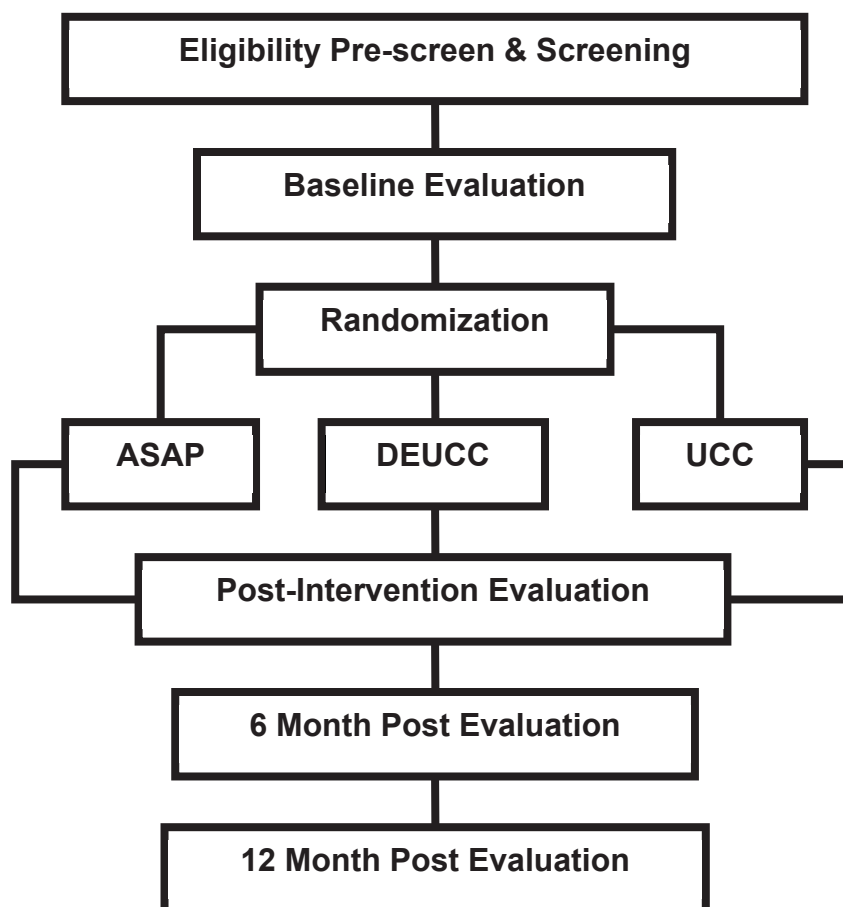


Figure 3.1: Overview of the I-CARE Design and Study Flow

ASAP = Accelerated Skill Acquisition Program; UCC = Usual and Customary Care; DEUCC = Dose-Equivalent Usual and Customary Care.

3.2 DESCRIPTION OF HOW THE DESIGN FULFILLS THE INTENT OF THE STUDY

Campbell and colleagues define a definitive Phase III randomized clinical trial of a complex intervention as one that, “compares a fully defined intervention with an ‘appropriate alternative’ using a protocol that is theoretically defensible, reproducible, and adequately controlled in a study with appropriate statistical power.”⁵⁷. The I-CARE trial is designed to compare ASAP, an integrated set of three essential elements (skill, capacity, motivation) bundled together in a theoretically defensible and reproducible task-specific training protocol, to an equivalent dose of usual and customary outpatient therapy. The dose-equivalent (DEUCC) control comparison is a particularly appropriate alternative given that: 1) the EXCITE design and findings do not rule out the possibility that usual and customary care provided at the same dose and intensity as CIT would have been as efficacious, 2) preliminary findings from VECTORS showed that a higher intensity of CIT applied acutely after stroke was not efficacious, while a lower intensity

of CIT yielded comparable results to a dose equivalent usual therapy group, and 3) well designed investigations of upper extremity rehabilitation in the outpatient setting, that compare the effectiveness of task-specific training to that of an equivalent dose of conventional therapy are sorely lacking^{30, 58, 59}. Finally, the non dose-equivalent, observation only group (UCC) will provide important information on the contents of standard outpatient therapy and empirical data on the provision of services that to our knowledge is unknown.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 INCLUSION CRITERIA

4.1.1 Disease Or Disorder Under Study, And How It Is To Be Documented

Diagnosis of stroke: Participants will be individuals with recent onset cerebral vascular accident, stroke event. A stroke is defined according to the World Health Organization (WHO) definition as, "a rapid onset event of vascular origin reflecting a focal disturbance of cerebral function, excluding isolated impairments of higher function and persisting longer than 24 hours." Clinical assessment and a CT or MRI scan will confirm the diagnosis.

4.1.2 Clinical Indicators Of Current Status, As Measured Within 7 Days Of Randomization

Inclusion and Exclusion criteria will be determined through chart review, participant interview and the physical screen performed by the Clinical Site Coordinator. Baseline evaluation will be used to confirm eligibility that might have changed during this dynamic period of recovery. The Physician Investigator will review inclusion and exclusion interview findings and provide documented clearance for participation in the study. If there is no confirmatory neuroimaging but all other inclusion/exclusion criteria are met, Dr. Dromerick, Principal Investigator and a board-certified neurologist, will review the available pre-screen, screen and medical records to confirm the clinical diagnosis of stroke based on the ICD-9 criteria and we will document the non-imaged status for tracking purposes.

Clinical Indicators for inclusion include:

1. 1) Ischemic or intraparenchymal hemorrhagic stroke without intraventricular extension with confirmatory neuroimaging, 28 and no more than 80 days after onset
2. age ≥ 21 and no upper limit
3. persistent hemiparesis leading to impaired upper extremity (UE) motor function: indicated by UE Fugl-Meyer⁶⁰ motor and coordination score no less than 19 out of 66 on the total motor score, but with at least a score of 1 on the hand item for finger mass extension/grasp release⁶¹
4. Evidence of preserved cognitive function: ≥ 4 on the FIM comprehension and problem solving score
5. No UE musculoskeletal injury or conditions that limited use prior to the stroke
6. Pre-stroke independence: Barthel Index⁶² no less than 95
7. Judged medically stable to participate as indicated by the patient's treating Physician or Physician Investigator

8. Expressed desire and ability by participant with confirmation by the family/caregiver to attend outpatient therapy 3x/wk for 10 wks and attend all follow-up evaluations

4.1.3 Prior Therapy

Participants will be pre-screened and screened as close to the beginning of rehabilitation as possible (within 5-75 days post stroke). They will have likely received one or a combination of physical therapy, occupational therapy and speech therapy during their acute and rehabilitation inpatient stay.

4.1.4 Demographic Characteristics As Applicable

Our Inclusion/Exclusion criteria are designed to capture the increasing number of surviving stroke patients who have a significant motor impairment, but whose deficit is not significant enough to prevent participation in an intense, focused therapy program. No inclusion/exclusion criteria will be based on gender, childbearing potential, and race or ethnic origin. Children and adolescents under the age of 21 will be excluded on scientific grounds. The incidence, etiology and pathophysiology of stroke are quite different in this age range, and inclusion would introduce substantial heterogeneity to the subject pool without providing a large enough sample to inform pediatric stroke care. More importantly, patterns of recovery differ with age, and adding small numbers of subjects with very different recovery from the target population would similarly impede hypothesis testing.

4.2 EXCLUSION CRITERIA

4.2.1 List Of Specific Clinical Contraindications

1. Previously been enrolled or currently enrolled in other rehabilitation or drug intervention studies
2. Living too far from the training site to participate reliably
3. Current major depressive disorder (defined by a score ≥ 3 on the PHQ-2)

4.2.2 Clinical/Laboratory Indicators Of Current Status, Obtained Within 7 Days Prior To Randomization

1. Mostly resolved UE hemiparesis indicated by: greater than 58/66 on the UE Fugl-Meyer⁶⁰ motor and coordination score
2. Ataxia out of proportion to weakness, NIHSS Ataxia > 0
3. Severe upper extremity sensory impairment indicated by anesthesia to light touch on the UE Fugl-Meyer sensation and proprioception
4. Neglect, as determined by NIHSS neglect item ≥ 1
5. Severe arthritis or orthopedic problems that limit passive ROM of upper extremity joints indicated by: shoulder flexion < 90 deg, shoulder abduction < 90 deg, shoulder external rotation < 45 deg, elbow extension < -20 deg, forearm supination and pronation < 45 deg from neutral, wrist extension < 0 deg, MCP and IP extension < -30 deg.
6. Pain that interferes with daily activities as indicated on the Pain Screen and pain score of 1 for at least 2 joints on the pain/ROM Fugl-Meyer UE assessment t

7. Balance and transfer function that requires more than contact-guard assistance

4.2.3 Specify Any Exclusion Related To Pregnancy Lactation Or Plans To Become Pregnant

Not applicable.

4.2.4 Use Of Excluded Drugs, Devices, Etc. Within 2 Days Prior To Study Entry

1. Receiving oral or injected antispasticity medications during study treatment

4.2.5 Specify Any Clinical (Life Expectancy, Co-Existing Disease), Demographic (Age) Or Other Characteristic That Precludes Appropriate Diagnosis, Treatment Or Follow-Up In The Trial

1. A history of psychiatric illness requiring hospitalization and/or diagnosis of Dementia
2. UE amputation

4.2.6 Active Drug Or Alcohol Use Or Dependence That, In The Opinion Of The Site Investigator, Would Interfere With Adherence To Study Requirements

1. History of sustained alcohol or drug abuse in the last 6 months

4.2.7 Serious Illness Until Participant Either Completes Therapy Or Is Clinically Stable On Therapy, In The Opinion Of The Site Investigator, For At Least 14 Days Prior To Study Entry

1. Pre-existing or concurrent neurological condition such as Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), or previous stroke with residual neurological deficits, or history of major head trauma
2. Not expected to survive 1 year due to other illness (cardiac disease, malignancy etc.)

4.2.8 Inability Or Unwillingness Of Participant Or Legal Guardian/Rep To Give Written Informed Consent

1. Inability to give informed consent for study participation

4.3 STUDY ENROLLMENT PROCEDURES

4.3.1 Identification And Recruitment Of Participants

Participants will be 360 women and men 21 years of age or older, recruited from among individuals with a diagnosis of stroke who are admitted to one of the study inpatient facilities or an affiliate facility or who have been discharged directly home from the acute facility, but with mild to moderate upper extremity impairments. Children, defined by NIH criteria as < 21 years have been excluded on scientific grounds. The incidence, etiology and pathophysiology of stroke are quite different in this age range, and inclusion would introduce substantial heterogeneity to the subject pool without providing a large enough sample to inform pediatric stroke care. More importantly, patterns of recovery differ with age, and adding small numbers of subjects with very different recovery from the target

population would similarly impede hypothesis testing. The expected demographics summarized in Table 4.3.1 by site and based on 2006 Rehabilitation Stroke Admissions represent those of the geographical areas participating in I-CARE. Our Inclusion/Exclusion criteria are designed to capture the increasing number of surviving stroke patients⁶³ who have a significant motor impairment, but whose deficit is not significant enough to prevent participation in an intense, focused upper extremity therapy program. Our criteria are relevant to the dimensions of motor impairment and participation including: medical stability, physiological stability, cognitive and motor capability and do not exclude a sizable proportion of stroke survivors who may have other common sequelae of stroke including depression. We carefully chose instruments that have a high level of specificity for I-CARE criteria. Based on previous work, the demographic and prognostic literature for UE recovery^{64, 31, 61, 65}, and the earlier timing (compared to EXCITE) for this intervention trial, we expect to capture the majority of eligible participants who otherwise might be overlooked in the current environment. Updated with 2005 statistics, Table 4.3.1 shows that between 62% and 80% of stroke admissions to our inpatient sites are discharged back to the community (home) and could be eligible for outpatient services.

The clinical site coordinator will pre-screen all stroke patients admitted to participating facilities as close to the beginning of rehabilitation as possible (within 5-75 days post stroke). Study options are presented while the patient is in the inpatient setting. The average inpatient stay for an uncomplicated stroke is 1 week for acute management and between 2 and 3 weeks for inpatient rehabilitation. The patient is usually discharged to home or to an extended care facility at this time, approximately 1 month from stroke onset. If the patient is a candidate for more rehabilitation, the option of outpatient rehabilitation is normally discussed with the patient just prior to their discharge. The timing and setting for the I-CARE study is therefore consistent with usual and customary care decision making about future rehabilitation needs. We expect that the informed consent will be presented close to the time of the patient's inpatient discharge and at the same time decisions about out-patient therapy are normally considered. If the patient does not want to make a decision about participation at this time, they will be given the opportunity to take the consent home and contact study staff at a later time, but prior to their 3 month anniversary from stroke onset should they wish to participate.

Enrollment will commence when the patient consents to the pre-screen procedure (no sooner than 5 days post-stroke) and usually during inpatient rehabilitation, prior to community discharge. The physician or clinical site coordinator will administer the NIHSS and Orpington Prognostic Scale. Pre-screen cut points that are prognostic for poor 1 month functional outcomes include > 5.2 on the Orpington Prognostic Scale⁶⁶. Reasons for exclusion will be recorded but no patient identifying information will be reported.

Candidates who pass the pre-screen will be introduced to the study by the Clinical Site Coordinator, provided a study Informed Consent to undergo a second screening assessment and requested to participate.

Participants who pass the pre-screen but fail to meet motor inclusion criteria at the study screen because they do not exhibit any distal voluntary movement of the hand will be followed prospectively out to 60 days post stroke to determine if there is a change in motor status that would make them eligible for inclusion.

If the patient passes the second screen and is deemed eligible > 2 weeks before the 1 month post-stroke anniversary, a follow-up telephone screen (assuming the patient is discharged home) will be conducted to: 1) confirm continued eligibility, 2) confirm willingness to participate, and 3) schedule baseline evaluation. The NIHSS will be repeated at baseline along with the Fugl-Meyer Upper Extremity (Motor) evaluation to confirm eligibility. Therefore, prior to randomization, participants will have completed the baseline evaluation and all relevant stratification variables entered into the I-CARE database via website.

After full compliance with all inclusion and exclusion criteria, medical clearance from the site Physician Investigator, and completion of the baseline evaluation, participants will be randomized to one of three treatment arms.

Table 4.3.1 Stroke Admissions, Demographics and Discharge Characteristics for Each Collaborating Center

Table 4.3.1 Stroke admissions, demographics, and discharge (DC) characteristics for each collaborating center							
Centers	DC	GA	CA				
Sites	NRH	CRM	CFRMC	CSMC	HRMA	LBMMC	RLANRC
2006 Rehab stroke admissions	466	249	248	210	94	171	422
% Female	51.07%	50.00%	54.84%	54.30%	44.68%	51.46%	37.70%
% White	25.97%	33.00%	20.67%	81.01%	72.34%	52.63%	11.99%
% African-American	67.17%	53.00%	53.51%	12.90%	7.45%	16.37%	20.14%
% Hispanic	2.15%	4.00%	0.00%	1.00%	3.19%	11.11%	52.76%
% Native Hawaiian or Other Pacific Islander	0.00%	0.00%	5.18%	0.00%	0.00%	1.23%	0.01%
% American-Indian	0.00%	0.00%	0.00%	0.01%	1.06%	0.00%	0.00%
% Asian	1.72%	1.00%	0.00%	5.21%	15.96%	11.70%	13.43%
% Other	3.00%	9.00%	20.64%	0.00%	0.00%	7.02%	0.00%
Mean age (yrs)	63.97	56	70.59	74	70	68.42	57.25
Age range (yrs)	15-97	18-88	—	31-105	30-95	26-96	18-89
% DC to home	72.53%	80.00%	74.60%	76.70%	63.83%	74.70%	76.30%
Mean Admission FIM per selected subgroup:							
Self Care	16.49	19.1	18.85	18.68	23.93	19	13.78
Mobility	5.96	7	11.56	12.05	7.24	7.4	8.7
Motor Subtotal	31.25	35.1	37.73	33.66	32.2	34	25.62
Cognitive Subtotal	24.88	20.6	18.11	21.51	22.5	17.9	18.35
Total FIM	55.95	55.6	55.84	57.28	56.71	53.7	45.17
Mean DC FIM per selected subgroup:							
Self Care	29.01	27.3	27.26	26.51	36.22	27.6	27.38
Mobility	13.27	12.4	18.55	23.28	13.71	12.6	20.24
Motor Subtotal	61.58	55.1	54.82	49.35	52.76	51.5	50.52
Cognitive Subtotal	27.92	24.6	20.79	23.39	25.14	21.5	22.17
Total FIM	89.63	79.7	75.61	76.57	82.30	77	76.65
Average rehab LOS	22.71	18	15.21	12	15.65	15.6	24.15
NRH - National Rehabilitation Hospital, Washington, DC							
CRM - Center Rehabilitation Medicine, Atlanta, GA							
CFRMC - Centinela Freeman Regional Medical Center, Inglewood, CA							
CSMC - Cedars-Sinai Medical Center, Los Angeles, CA							
HRMA - Huntington Rehabilitation Medicine Associates, Pasadena, CA							
LBMMC - Long Beach Memorial Medical Center, Long Beach, CA							
RLANRC - Rancho Los Amigos National Rehabilitation Center, Downey, CA							
FIM - Functional Independence Measure (functional item scores range from 1 Total Assistance to 7 Independent; note 4 = Minimum Assistance)							

4.3.2 Procedures For Documentation Of Reasons For Ineligibility And For Non-Participation Of Eligible Participants

If participants are excluded, reasons for exclusion will be recorded but no patient identifying information will be reported.

4.3.3 Consent Procedures

Both a HIPAA release document and screening informed consent will be attained to collect pre-screen and screen data. Candidates who meet initial criteria will be introduced to the study by the Clinical Site Coordinator, requested to participate, and be provided with a study specific Informed Consent Form. Please refer to section 4.3.1 for details about timing and setting for the explanation of the study and obtaining informed consent.

4.3.4 Description Of Procedure For Obtaining Intervention Group Assignments

After full compliance with inclusion and exclusion criteria, medical clearance from the site Physician Investigator, and completion of baseline evaluations, a total of 360 participants will be randomized. Patients randomized to either ASAP or DEUCC will undergo 30 hours of one-on-one outpatient therapy distributed over a 10 week duration that best accommodates the patient and clinician's schedule. Patients randomized into UCC will be observed only during the prescribed out-patient occupational therapy. Treatment allocation will occur after baseline assessment no earlier than 28 days and no later than 75 days post-stroke.

5 STUDY INTERVENTIONS

5.1 INTERVENTIONS, ADMINISTRATION, AND DURATION

The three interventions, ASAP, DEUCC and UCC, will take place at the clinical site outpatient clinic.

5.1.1 Accelerated Skill Acquisition Program (ASAP) Intervention

The Accelerated Skill Acquisition Program (ASAP) training intervention is a fully defined protocol that is based on the fundamental elements of **skill** acquisition through task-specific practice, impairment mitigation to increase **capacity**, and **motivational** enhancements to build self-confidence. It is grounded in the following evidence-based principles: Effective rehabilitation of the paretic upper extremity is achievable and based upon the provision of challenging, intensive, and meaningful task practice for motor skill acquisition, mitigation of associated linchpin impairments and dysfunctions of movement, and the confidence to integrate use of emerging skills into daily life^{5, 15, 16, 64, 67}. Eight principles are used to guide ASAP intervention sessions: 1) Ensure challenging and meaningful practice^{16, 28, 29, 68, 69}, 2) address important mutable impairments⁷⁰⁻⁷³, 3) enhance motor capacity through overload and specificity^{74, 75}, 4) preserve natural goal-directedness in movement organization^{76, 77}, 5) avoid artificial task breakdown when engaging in task-specific practice⁷⁸, 6) active patient involvement and opportunities for self-direction are feasible and desirable^{54, 79}, 7) balance immediate and future needs for efficient motor skill and capacity enhancement with the development of confidence and self-management skills^{80, 81}, and 8) drive task-specific self-confidence (self-efficacy) high through performance accomplishments⁸².

ASAP protocol parameters: The program begins with an orientation session to 1) prepare the collaborative real-world task list to be used during training; it includes 4-5 tasks the patient most wants to perform with at least one a bimanual activity, one a strength-dependent activity including the most-affected arm, and one activity requiring

dexterity of the most affected hand, 2) designate a priority or benchmark task from the collaborative task list, 3) determine fundamental impairments and the challenge point(s) or breakdown point(s) for a minimum of the priority/benchmark task, 4) prepare a collaborative schedule for the first day of training, 5) orient the participant to the mitt and its function, 6) identify appropriate conditions for mitt wearing, 7) orient the participant to the brief self-efficacy question, 8) orient the participant to out-of-lab action plans (i.e., homework), 9) orient the participant and trainer to roles during the 10-weeks of training, and 10) obtain participant signature on the collaboration agreement. Training sessions are 3x per week for a total of 30 hours, with rest breaks as needed, but kept to a minimum. The training session begins with collaborative ordering of the real-world tasks identified at the orientation session. The real-world tasks may change as interests and goals evolve, however the priority task may not change. Task and movement analysis is done for each real-world task to determine the key movement dysfunctions or impairments. The goal of intervention training is to focus attention and effort directly on the problematic area (i.e. dysfunction, impairment) to facilitate skill acquisition without simply providing a compensatory strategy as a quick fix to the problem. Classic physiologic-like overload parameters are used to drive progress. Practice activities within real-world tasks are selected based on patient perspective/preference. Training is collaborative and interactive with the participant actively participating in problem solving and assessing performance. Confidence building and empowerment is embedded in the training and education. Self-efficacy assessment is done 4 times throughout the training period using the Brief Self-Efficacy Rating Scale and asking “on a scale of 0-10, how confident are you that you can (fill in specific Priority activity)?” This is followed by a question asking, “What can we do this week to make you more confident?” Participants will be asked to sign a collaborative agreement contract. Included in their responsibilities is to perform inter-session ‘action plans’ or out of lab activities. The assignments encourage specific practice in the home or community setting. Examples include finding a challenging task involving food preparation or eating or reading an education handout about motor recovery. Participants are asked to report on the effectiveness of their action plan assignment on the next day of training before the practice session begins that day.

ASAP Schedule: ASAP includes 30 hours of one-on-one training delivered over 10 weeks.

5.1.2 Usual and Customary Care Therapy (UCC)

Participants who are randomized to UCC will be treated by a licensed and experienced occupational therapist working in the outpatient setting. The therapists are free to design and implement treatment according to their usual practice. We will require a minimal documentation burden and monitor treatment throughout the UCC interval. This is an observation only group with no a priori stipulation of the number of visits. Documentation is similar for UCC and DEUCC.

UCC Schedule: UCC includes one-on-one training delivered per the participant’s therapy prescription.

5.1.3 Dose-Equivalent Usual and Customary Care Therapy (DEUCC)

While several studies describe and evaluate usual occupational therapy during inpatient rehabilitation⁸³⁻⁸⁶, we identified no published study that documents such therapy specifically in the post-acute outpatient context. Further, Medicare records indicate that the quantity of outpatient care is rapidly changing, partially in response to the Balanced Budget Act of 1997 and its sequelae⁸⁷. We conducted an informal survey of 25 licensed Occupational Therapists working in outpatient, hospital-based settings across the country to determine standard therapeutic practices for individuals post-stroke, with emphasis on recovery of upper extremity function. Sixty percent of the survey respondents had greater than 10 years of clinical experience, and almost three-quarters had been practicing for at least 5 years. Therapists were asked to write-in the typical interventions employed, based on their experiences and practices of their colleagues. Analysis of responses revealed 5 major categories of post-stroke UE intervention: 1) Functional Task and I/ADL training (21 respondents=84%), 2) Posture and neuromuscular rehabilitation (20 respondents= 80%), 3) Weight-bearing and strengthening activities (19 respondents=76%), 4) Range of Motion exercises (12 respondents= 48%), and 5) Modalities (stimulation, ice, heat, etc.) (19 respondents=76%). These results are consistent with the American Occupational Therapy Association (AOTA) published practice guidelines for adults with stroke. AOTA guidelines specify that "the goal of therapy is to increase "function" and "intervention addresses both the component deficits [such as postural and motor control, muscle strength and tone] and the context of the client's life". Furthermore, the guidelines list treatment techniques for adults with stroke, including: Functional mobility training, Compensatory techniques for ADL, Neuromuscular facilitation and inhibition techniques, Motor control retraining, Weight-bearing techniques, Strength and endurance techniques, Self range of motion techniques, and Physical agent modalities. We expect the DEUCC intervention for I-CARE to be representative of a typical UE intervention for adults with stroke, as supported by both these national practice guidelines and our survey results of clinical practice.

DEUCC Protocol Parameters: Participants who are randomized to this group will be treated by a licensed and experienced occupational therapist working in the outpatient setting. The therapists are free to design and implement treatment according to their usual practice. We will require a minimal documentation burden from the therapist. The number of visits is constrained to 30 to comply with the ASAP therapy dose. The site coordinator will inform the treating therapist of this stipulation only after the prescriptive dose has been determined and documented. The site coordinator or designated research assistant will monitor the actual number of visits, document it and the contents of the therapy sessions as described in the MOP

DEUCC Schedule: DEUCC includes 30 hours of one-on-one training delivered over 10 weeks.

5.2 HANDLING OF STUDY INTERVENTIONS

5.2.1 Standardization Procedures For The Investigational Intervention Group

Evaluation of training procedures is important for: 1) assuring standardization across study sites; 2) providing feedback from the training center to all site personnel concerning administration of techniques; and 3) providing possible explanations for I-CARE results in the event of non-standard administration. The standardization process including initial training and maintenance throughout the trial is detailed in the Manual of Procedures (MOP). It is designed to provide constructive feedback to personnel and ultimately improve their performance with the protocol administration. Briefly, the initial training includes a two phase process with Phase 1 competency tested at the conclusion of a 3-day training workshop held during the start-up phase. A schedule for the completion of Phase II competency will be developed prior to the end of the Phase I training meeting.

A MOP will be disseminated to the Administrative Coordinating Center, the Data Management Center, and to each clinical intervention site. The MOP is under revision and will be finalized within the first year of the study during start up. It includes all details for the intervention protocols, standardization training procedures, instructions on measures, and all data collection forms (clinical report forms). Use of the MOP as well as regular monitoring site visits will ensure systematic delivery of the investigational intervention across sites.

Training of all intervention therapists will occur during the initial six months of the study (**Table 5.2.1**).

The initial training activity will be led by the ASAP Intervention Team (Blanton, Pate, Lewthwaite, Winstein, and Wolf). ASAP intervention therapists (clinical site coordinators) will attend a 3-day training workshop in Los Angeles to accomplish Phase I competency in administration and documentation of a complete dose (30 hrs). For Phase II competency, each interventionist will be videoed, off-site during administration of each element (task-specific training; impairment mitigation; motivational enhancements) with study volunteers. Follow-up videotapes of the intervention therapist are required once a month for the first three months after the beginning of participant enrollment, once again three months later, and once every six months for the remainder of the project.

Table 5.2.1 I-CARE Gantt Chart

Table 5.2.1 I-CARE Gantt Chart					Trial Timeline																			
					Year 1				Year 2				Year 3				Year 4				Year 5			
Quarters	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4				
Manual of procedures finalized																								
Standardization training and certification (all three groups)																								
Web based data entry and tracking finalized																								
HIPAA and IRB approval (all sites)																								
Monitor Usual Occupational Therapy																								
Staff recruitment																								
Supplies/Equipment procured																								
Field training (data entry etc.)																								
Recruitment material																								
Participant recruitment																								
Intervention and follow-up																								
Data analysis (interim analysis)																								
Publication preparation																								
The gray areas indicate the period in which the activities are performed.																								

Evaluation of all training videotapes will be conducted by the ASAP Intervention Team. We will use the consensus model approach where a rater pair observes a set of videotapes. They subsequently discuss each performance observed and, by consensus, provide one rating for each category on the administration rating sheet. As a general rule, each panel (2 individuals) observes a videotaped segment of the tape, discusses the performance, and decides upon the most appropriate rating for the videotaped segment. Individuals selected for the panels will be either longstanding members of the EXCITE research project here at USC or with experience conducting examinations and applying rehabilitation interventions in other studies to persons with neuromuscular dysfunction. New panel members will be trained by the Training Center Director (Patricia Pate, MPT) or Co-Director, (Sarah Blanton, DPT). Once rated, the completed recording sheets and summary of results will be returned to the individual rated via email with a record kept at the training center. Additionally, the results will be shared with the site Physician Investigator. All results will be monitored and further analyzed by the I-CARE Training Center staff. To gain approval for administration of ASAP, the performance of a site must be equal to or greater than 90% criterion. Standardization will continue throughout the duration of the study. The Clinical Research coordinator and Principal Investigators are responsible for maintaining standardization and competency throughout the trial. All new staff or back-up intervention therapists will be required to procure full certification before being allowed to administer the investigational treatment.

Standardization will continue throughout the duration of the study. Specific filming procedures are described in the MOP. The expected frequency of requests is as follows: 1) once a month for the first three months of participant enrollment, 2) once again three months later, 3) once every six months for the remainder of the project. The Clinical Site Coordinator and Principal Investigators will be responsible for maintaining standardization and competency throughout the trial.

Communication among the site lead trainers with the Principal Investigators will be maintained through conference calls to review and discuss any training questions, adverse events, or other concerns. An email list-serv will provide timely responses to questions from the training teams with responses available to all training personnel. This list of questions and responses will be recorded throughout the trial and used to refine or clarify issues in the training manual. The Clinical Site Coordinators will conduct routine on-site visits every month to each site and relay any intervention-related concerns to the Principal Investigators.

5.3 CONCOMITANT INTERVENTIONS

5.3.1 Required Interventions

Since the possibility exists that following randomization, participants may seek additional or other treatments, we will monitor those options and acquire data on a monthly basis during the one year of participant commitment to I-CARE. Acquiring this information is important, because additional physical or pharmacological treatments could impact changes in primary and secondary outcomes. Upon enrollment, each individual will be given a notebook containing a calendar notifying them of subsequent appointment dates. The notebook will also contain another calendar housing a check list including all interactions with any health care provider and all medications and devices. No stimulants or antispasticity medications will be allowed during the study related treatments; their use afterwards will be neither encouraged nor discouraged, but will be recorded for use in secondary analyses. Antidepressant use is not exclusion, but will be monitored for secondary analyses. All complications (including those which would have caused exclusion from the study had they occurred prior to randomization) and resulting treatments will be recorded, but such individuals will remain in the study because of the intent-to-treat analysis plan. The calendar is constructed so that patients need only check the type of intervention and where relevant, the dosing. The information will be conveyed to site teams through monthly phone calls and scheduled re-evaluations. This procedure was employed successfully at the Emory EXCITE, and the USC Northstar EVEREST coordination sites. This is where we will monitor all drug therapies that we expect could be extensive based on our proof of principle data.

5.4 ADHERENCE ASSESSMENT

Tracking compliance during the intervention for those randomized to ASAP will be done at two levels: 1) compliance with the schedule of visits up to 30 hours and 2) compliance with out-of-laboratory action plans. The latter will be accomplished through a brief discussion at the beginning of the next visit regarding the “out-of-lab” action plan assignment and mitt use. The patient will be expected to report the results of their assignment and any mitt use and to keep a log of each during the intervention interval. In the unlikely event that participants fail to engage in action plan activities, we will compile reasons for such failures. Adherence to post-intervention action plans will be assessed during monthly phone calls at which time the interviewer will ascertain the extent to which each participant has continued and progressed the activities he/she determined at the end of the outpatient visits. In an effort to monitor out-of-therapy arm use for all groups, we will devise a check list that will be collected monthly (calendar format) during our follow-up calls to define amount of time estimated to have been spent

using the impaired arm daily. While fraught with problems regarding accuracy, it is the most “real” and cost effective way to do so. We will simply examine estimates of use over time. Intervention therapists will provide a rating of the extent of likely engagement of the participant in significant upper extremity practice outside the training setting as a function of the participant’s description of activities, identification of successes and barriers to be addressed, and demonstration of practiced movement behaviors. Patient self-reports of outside activity will also be obtained from all participants in each study arm through exit instruments.

6 CLINICAL AND LABORATORY EVALUATIONS

Primary Outcome Measure: Wolf Motor Function Test (WMFT)

The Wolf Motor Function Test (WMFT)¹ determines the time required for patients with stroke to perform 15 everyday tasks with each upper extremity. Over the past 6 years, this measure has been used as either a primary or secondary outcome in at least 55 published studies. Performance time (up to 120 seconds), strength (in lbs for lifting and in kgs for hand grip), and quality of motor function based upon a 6-point scale Functional Activity Scale⁸⁸ are assessed. Tasks are sequenced so that the first seven tasks involve simple limb movements, primarily of the proximal musculature; the next ten tasks require manipulation and distal control. Many of the tasks are modified from the Jebsen-Taylor hand function test⁸⁹. Reliability for the Jebsen test was established by the original authors and grip strength reliability has also been reported by Mathiowetz and colleagues⁹⁰. The reliability and validity of this test are: inter-rater reliability - correlation coefficient > .80 and validity, $\pm 3\%$ accuracy for the Jamar dynamometer⁹⁰. Each WMFT task is defined by a specific, detailed “anchoring” definition. For each task, information regarding patient positioning, placement of objects to be targeted or manipulated, distance of the participant to the object, whether seated or standing, and verbal instructions have all been operationalized.

Secondary Outcome: Measure-Self Reported Paretic Hand Function – SIS Hand Function

The Stroke Impact Scale (SIS) is a full spectrum health status inventory. It is a stroke-specific, self-report measure composed of 59 items which are distributed in eight separate domains (strength, hand function, mobility, activities of daily living, emotion, memory, communication, and social participation). The SIS hand function domain is: 1) a valid and reliable measure that is well aligned with I-CARE specific aims, 2) it has face validity for clinical meaningfulness, 3) we acquired estimates of the ‘natural’ change in SIS hand function during the acute and post-acute period when dynamic change is high and I-CARE intervention occurs (Sec 4.3), and 4) this self-report measure of hand function corresponds well with our primary laboratory-based outcome of performance.

Secondary Outcome Measure: Full Spectrum Stroke Impact Scale

The full SIS will be administered at Baseline, Post-Intervention and both Follow-up evaluations. While the specific effects of the treatment intervention are expected to influence the hand function domain the most, we also expect several non-specific effects on health status generally and the composite physical performance and social

participation domains contained in the full SIS. This was true for the EXCITE trial and we expect similar findings for I-CARE.

Other Secondary Outcome Measures

A full battery of other measures will be taken at each evaluation point that will provide complementary information about muscle strength, functional ability, depression, self-confidence, life satisfaction, reintegration, and subjective quality of life. The specific tests are detailed in the MOP, but listed here for completeness under the International Classification of Function and Disability Framework⁹¹. **Body Function/Body Structure:** Arm muscle torque⁹², UE Fugl-Meyer (Motor)⁶⁰, depression (9-item self-report Patient Health Questionnaire-9)^{93, 94}, and 20-item Confidence in Arm and Hand Movements (CAHM). **Activity:** Action Research Arm Test (ARA)⁹⁵, TEMPA^{96, 97}, and Motor Activity Log-MAL-28-QOM⁹⁸. **Participation:** Reintegration to Normal Living Index (RNLI)^{99, 100}, Satisfaction with Life Scale (SWLS)¹⁰¹⁻¹⁰³, Single item subjective quality of life (SQOL)^{104, 105}, and Exit Interview.

6.1 SCHEDULE OF EVALUATIONS

We have selected measures that have established reliability and validity. A Table of study measures, variables and data; protocol books for acquisition of measures; and data collection forms are in the Tests and Measures category of the MOP. Staff blinded to group assignment will perform all evaluation measures. Evaluation therapists will generally be per diem (FFS) trained and certified clinicians (having passed the standardization certification), and are not part of the intervention team. They will be unaware of treatment assignment and will conduct each baseline and follow-up assessment. The Site Coordinators will work with each participant to assure they are well-educated to refrain from discussing assignment group with the evaluator. All evaluation and follow-up measures will be performed at a different physical location than where the intervention will be administered, further reducing the risk of unblinding. To determine the effectiveness of our single blinded assessments, we will ask both the therapists and participants to complete a brief assessment to determine if group assignment was revealed during the evaluation. All incidents of unblinding will be documented as a protocol violation.

Table 6.1 Schedule of Evaluations

EVALUATIONS	Screen	Baseline	Randomization	Post Intervention	6-mo Post	12-mo Post
Days post stroke	5-72	28-72	28-74	60-145	249-338	426-521
Weeks post randomization				5-11	31-37	57-63
HIPAA Release	x					
Screen Informed Consent	x					
Chart Review	x					
NIH Stroke Scale	x					
Orpington Prognostic Scale	x					
Patient Interview	x					
Barthel Index	x					
Physical Screen	x					
MD Screen and approval	x					
Collect contact and demographic information	x					
Follow-up phone screen		x				
Issue study timeline, site specific phone numbers, maps, transportation information			x			
Video Tape consent		x				
Primary Outcome						
WMFT (time)		x		x	x	x
Secondary Outcomes						
Body Structure/Body Function						
Arm Muscle torque/grip/pinch		x		x	x	x
WMFT strength items		x		x	x	x
UE Fugl-Meyer (Motor)	x	x		x	x	x
PHQ-2		x		x	x	x
CAHM		x		x	x	x
Activity						
SIS (Hand)	x	x		x	x	x
WMFT FAS		x		x	x	x
ARA		x		x	x	x
TEMPA		x		x	x	x
MAL-28 (QOM)		x		x	x	x
Participation						
RNLI		x		x	x	x
SWLS		x		x	x	x
Single Item SQOL		x		x	x	x
End of Study Exit Interview						x
Comprehensive of Body Structure/Function, Activity and Participation						
Full SIS		x		x	x	x
Non-outcome Monitoring						
Physiologic Measures		x		x	x	x
Physical Exam		x			x	x
Post Intervention Exit Interview				x		

6.2 TIMING OF EVALUATIONS

This section includes definitions of the column headings in Table 6.1, Schedule of Evaluations.

6.2.1 Pre-Randomization Evaluations

These evaluations occur prior to the participant receiving any study interventions.

6.2.1.1 Pre-Screen

Participants will be pre-screened and enrolled 5-30 days post stroke. To determine eligibility, the clinical site coordinator will perform an initial pre-screen on all stroke patients admitted to participating facilities. The physician or clinical site coordinator will administer the NIHSS and Orpington Prognostic Scale. Pre-screen cut points that are prognostic for poor 1 month functional outcomes include > 5.2 on the Orpington Prognostic Scale⁶⁶. Reasons for exclusion will be recorded but no patient identifying information will be reported. Candidates who pass will be introduced to the study by the clinical site coordinator, provided a study Informed Consent to undergo a second screening assessment and requested to participate.

6.2.1.2 Screen

Participants will be screened and enrolled as close to the beginning of rehabilitation as possible (within 5-72 days post stroke). Candidates who meet initial pre-screen criteria will be introduced to the study by the clinical site coordinator, be requested to participate, and be provided a study Informed Consent.

If the patient passes the second screen and is deemed eligible > 2 weeks before the 1 month post-stroke anniversary, a follow-up telephone screen (assuming the patient is discharged home) will be conducted to: 1) confirm continued eligibility, 2) confirm willingness to participate, and 3) schedule baseline evaluation. The UE Fugl-Meyer will be repeated at baseline to confirm eligibility. Therefore, prior to randomization, participants will have completed the baseline evaluation and all relevant stratification variables entered into the I-CARE database via website.

6.2.1.3 Baseline Evaluation

Participants will attend a baseline evaluation 28-72 days post stroke. The baseline evaluation consists of the primary outcome measure of the Wolf Motor Function Test (WMFT) and secondary outcome measures that fall within the international classification system of Body Structure/body Function, Activity and Participation. Non-outcome measures will be taken including vitals.

6.2.1.4 Randomization

Upon successful completion of the baseline evaluation, participant will be stratified and randomized to one of three intervention groups.

6.2.2 On-Study Evaluations

There are no formal evaluations for the purpose of outcome measures scheduled during the intervention period.

6.2.3 Post-Intervention Evaluations And Final Evaluation

There are three scheduled follow-up time points. The first will immediately post intervention (approximately 60-145 days post stroke). The second follow-up evaluation (FU1) will occur at 6 months post intervention (239-328 days post stroke). The final follow-up evaluation (FU2) will be conducted 12 months post intervention (419-514 days post stroke). At the final evaluation (FU2) participants will be asked a set of questions provide manipulation checks or that addresses the extent to which critical components of interventions (e.g., interfering impairments, challenging workloads, participant chosen tasks, and self-efficacy) were incorporated in the assigned intervention ¹⁰⁶. Participants will also be asked to report the perceived value of the intervention. At the 1-year time point, study exit questions will focus on overall impact of the study as well as participants' activity between the end of intervention and the end of the study.

6.3 SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS

The following is a brief description of the rows of the Table 6.1 Schedule of Evaluations.

6.3.1 HIPAA Release

This is the standard HIPAA release and can be found in [section 2.I.3](#) of the MOP.

6.3.2 Screen Informed Consent

The clinical site coordinator will consent the potential participant. Please refer to [section 2.I.1-2.I.2](#) of the MOP for a description of the informed consent process and to view the Screen Informed Consent document.

6.3.3 Medical Letter of Approval

A letter describing the I-CARE study will be sent to the potential participant's primary physician requesting approval to participate in the research study. Please refer to [section 2.S.2.11](#) of the MOP for the full letter.

6.3.4 NIH Stroke Scale

Please refer to [section 2.M.2.1.1](#) of the MOP for instructions on how to administer the NIH Stroke Scale and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.5 Orpington Prognostic Scale

Please refer to [section 2.M.2.1.2](#) of the MOP for instructions on how to administer the Orpington Prognostic Scale and [section 2.S.2.11](#) for the CRF.

6.3.6 Chart Review

Potential participant chart's are reviewed for information regarding age; gender; contact information; ischemic or intraparenchymal hemorrhagic stroke without intraventricular extension; confirmatory neuroimaging; evidence of preserved cognitive function (indicated by ≥ 4 on the FIM comprehension and problem solving score); history of significant depression, psychiatric illness requiring hospitalization and/or diagnosis of Dementia; pre-existing or concurrent neurological condition such as Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), or previous

stroke with residual neurological deficits, or history of major head trauma; history of sustained alcohol or drug abuse in the last 6 months; receiving oral or injected antispasticity medications during study treatment.

6.3.7 MD Screen

The clinical site physician will conduct a medical screen to confirm medical stability. Please refer to [section 2.S.2.11](#) of the MOP for the CRF.

6.3.8 Patient Interview

Specific inclusion/exclusion items to be covered during the patient/family interview include: expressed desire and ability by participant with confirmation by the family/caregiver to attend outpatient therapy 3x a wk for 10 weeks, and attend all follow-up evaluations; whether if the potential participant has previously been enrolled or currently enrolled in other rehabilitation or drug intervention studies; and if the potential participant lives too far from the training site to participate reliably.

6.3.9 UE Fugl-Meyer (Motor)

The UE Fugl-Meyer motor section includes component tests of reflexes, active motion, and coordination. The motor section has a maximum score of 66 and measures reflexes, volitional movement including flexor/extensor synergies, movement combining synergies, movement out of synergy, stability and movement of wrist and hand, and coordination/ speed. Please refer to [section 2.M.2.1.3](#) of the MOP for instructions on how to administer the UE Fugl-Meyer (Motor) and [section 2.S.2.11](#) of the MOP for the CRF.

6.3.10 Mini-Cog

This is a test of cognition in which the participant must recall 3 randomly assigned words following a distraction task of drawing a clock. Please see [section 2.M.2.1.4](#) of the MOP for instructions on how to administer the Mini-Cog and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.11 Barthel Index

This is a measure of pre-stroke function. Please see [section 2.M.2.1.5](#) of the MOP for instructions on how to administer the Barthel Index and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.12 Physical Screen

The Physical Screen includes measures of vitals; goniometric measures of active and passive upper extremity range of motion; pain; spasticity using the Ashworth Scale; and mobility. Please see [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.13 Inclusion/Exclusion Checklist Form

This is a summary form documenting eligibility. Please see [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.14 Follow-up Phone Call

The clinical site coordinator or the research assistant will place a follow-up phone call to the participant to ensure eligibility in the study and answer any questions.

6.3.15 Study Informed Consent

If the potential participant continues to be eligible for the study, the clinical site coordinator will explain the study in more detail and consent the potential participant. Please refer to [sections 2.I.1-2.I.2](#) of the MOP for a description of the informed consent process and to view the Study Informed Consent document.

6.3.16 Primary Outcome Measure

6.3.16.1 Wolf Motor Function Test (WMFT)-Time

This test consists of 17 items, 2 of which involve strength measures and 15 of which involve timed performance on various tasks. The tasks are sequenced by complexity and the number of joints primarily responsible for task completion. The first seven tasks involve simple limb movements, primarily of the proximal musculature; the next ten tasks require manipulation and distal control. Performance time (up to 120 seconds) is measured. Quality of movement based upon a 6-point scale Functional Activity Scale⁸⁸ (FAS) are assessed. Please see [section 2.M.2.1.9](#) of the MOP for instructions on how to administer the WMFT and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.17 Secondary Outcome Measures: Body Structure/Body Function

Body Structure/Body Function is one domain within the International Classification System.

6.3.17.1 Arm Muscle Torque Test

Maximum isometric torque will be tested for six isometric positions using the hand held Nicholas MMT dynamometer and standard testing positions. The MMT test consists of isometric “make contractions” in which the patient uses each tested muscle group to push maximally against the curved plate and the piston of the hand-held device for 4-5 seconds. Each muscle group will be tested three times and the highest score will be used. Please see [section 2.M.2.1.7](#) of the MOP for instructions on how to administer the Arm Muscle Torque Test and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.17.2 WMFT- Strength Items

Strength is measured in lbs for lifting, and in kgs for hand grip. Please see [section 2.M.2.1.9](#) of the MOP for instructions on how to administer the WMFT and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.17.3 UE Fugl-Meyer (Motor)

See section 6.3.9 above for description.

6.3.17.4 PHQ-2

Depression constitutes a secondary outcome of interest in the proposed I-CARE study. Impact of the upper extremity interventions on depression will be measured with the 2-item self-report Patient Health Questionnaire-2 (PHQ-2)¹⁰⁷⁻¹¹⁰ reflective of current DSM-IV and ICD-10 criteria for diagnosis of depressive disorders and developed to screen and diagnose depression in individuals in primary care settings. It has been used in a NINDS-funded study⁹⁴ to screen for depression in the I-CARE identical 1- to 3-month post-stroke interval and has been found responsive to treatments for depression in a multisite treatment trial of late-life depression⁹³. Respondents report the frequency (from 0, not at all, to 3, nearly every day) that they have experienced each of 9 depressive symptoms during the previous 2 weeks. Scores are summed to create a summary scale score that can range from 0 (no depressive symptoms) to 27 (all symptoms occurring nearly daily). A minimal clinically important difference for individual change has been established as 5 points on the 0 to 27 point PHQ-2 scale⁹³. The PHQ-2 will be administered at baseline, immediately post-intervention, at 6 months post intervention, and at the 1-year post-intervention assessment. Please see [section 2.M.2.1.8](#) of the MOP for instructions on how to administer the PHQ-2 and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.17.5 Confidence In Arm And Hand Movements (CAHM)

The 20-item Confidence in Arm and Hand Movements¹¹¹ scale was designed to examine self-efficacy or confidence for arm and hand function in individuals following stroke in home (e.g., “How certain are you at the present time that you can open a large-mouth jar?”) and community or public contexts (“How certain are you at the present time that you can cut food with a knife and fork at a restaurant?”). Items refer to unimanual and bimanual activities and are scored on a 0 (very uncertain) to 100 (very certain) scale and averaged to provide a total score ranging from 0 to 100. Preliminary evidence of instrument reliability and validity is strong. Please see [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.18 Secondary Outcome Measures: Activity

Activity is a domain within the International Classification System.

6.3.18.1 Stroke Impact Scale (Hand function) version 3.0-Hand

The Stroke Impact Scale (SIS) is a full spectrum health status inventory. It is a stroke specific, self-report measure composed of 59 items which are distributed in eight separate domains (strength, hand function, mobility, activities of daily living, emotion, memory, communication, and social participation). The SIS hand function domain is: 1) a valid and reliable measure that is well aligned with I-CARE specific aims, 2) it has face validity for clinical meaningfulness, 3) we acquired estimates of the ‘natural’ change in SIS hand function during the acute and post-acute period when dynamic change is high and I-CARE intervention occurs, and 4) this self-report measure of hand function corresponds well with other laboratory-based measures of performance. Please see [section 2.M.2.1.6](#) of the MOP for instructions on how to administer the SIS and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.18.2 WMFT Functional Ability Scale (FAS)

Quality of movement based upon a 6-point scale Functional Activity Scale⁸⁸ (FAS) are assessed. Please see [section 2.M.2.1.9](#) of the MOP for instructions on how to administer the WMFT and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.18.3 Action Research Arm Test (ARA)

The ARA is a functional assessment of strength and coordination. Derived from the Fugl-Meyer scale, the ARA includes 19 items divided into four subscales: grasp, grip, pinch, and gross movement. The items within each subtest are ordered based on a Guttman scale from most to least difficult. The most difficult item is presented first, reducing administration time if the participant can successfully complete that item. The Guttman scaling assures that the easier items would also be successfully completed. Reliability, construct validity, and predictive validity of the ARA have been well established. Test-retest reliability is 0.98-0.99 on the subscales; internal consistency ranged from 0.94-0.98. The ARA uses ordinal scoring for each subtest item. Item scores are summed to create subtest and a full-scale score. Several randomized controlled trials of CIT have used the ARA and found statistically significant treatment effects. Please see [section 2.M.2.1.10](#) of the MOP for instructions on how to administer the ARA and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.18.4 TEMPA

The TEMPA is a 9 item functional ability measure with both unimanual and bimanual tasks. Tasks include gross motor and fine motor movement such as reaching for a pitcher of water and pouring to coin and small object manipulation. Each task is timed and graded on a 4 point ordinal functional ability scale of (0 = successful completion-no difficulty, -3 = task cannot be performed >25%). Please see [section 2.M.2.1.11](#) of the MOP for instructions on how to administer the TEMPA and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.18.5 MAL-28 (QOM)

MAL-28-QOM a structured interview intended to examine how well the participant uses the more affected arm outside of the laboratory setting. Participants are asked 28 standardized questions about the quality of their movement during the functional activities indicated ("How Well" Scale or HW). The scale is printed on a separate sheet of paper and placed in front of the participant during test administration and ranges from 0 – 5 with 5 indicating normal or the same as pre-stroke. Participants should be told that they can give half scores (1.5 etc, show them the scales) if this is reflective of their ratings. Please see [section 2.M.2.1.12](#) of the MOP for instructions on how to administer the MAL-28 (QOM) and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.19 Secondary Outcome Measures: Participation

Participation is a domain within the International Classification System.

6.3.19.1 Reintegration To Normal Living Index (RNLI)

The Reintegration to Normal Living Index (RNLI) was designed for use in follow-up assessments of individuals with a limiting physical or cognitive condition. The goal of

this scale is to help document how a person is able to resume normal life activities after an incapacitating injury or illness. The RNL assesses global function and measures the individual's satisfaction with basic self-care, in-home mobility, leisure activities, travel and productive pursuits. Individuals respond to 11 statements used to assess reintegration into their pre-insult pattern of living. The scale has high internal consistency and interrater reliability. Construct, content and predictive validity have also been established. This assessment is based on an 11-55 total score range, wherein a lower score indicates a higher attainment of normal levels of living. Please see [section 2.M.2.1.13](#) of the MOP for instructions on how to administer the RNL and [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.19.2 Satisfaction With Life Scale (SWLS)

The Satisfaction with Life Scale (SWLS) ¹⁰² is a 5-item scale that assesses participants' overall life satisfaction without explicit reference to particular domains such as health, activities, or role-related functioning (e.g., "The conditions of my life are excellent."). Responses to each item can range from 1 = strongly disagree to 7 = strongly agree. The SWLS has demonstrated validity and reliability and has been used in a variety of patient and non-patient samples ^{101-103, 112}. Higher scores indicate higher perceived life satisfaction. [Please see section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.19.3 Single Item Subjective Quality Of Life (SQOL)

The Subjective Quality of Life measure ¹⁰⁵ is a single-item rating of participant perception of overall quality of life, distinct from satisfaction with life or explicit health-related quality of life. Respondents rate their quality of life on a visual analogue scale anchored by the phrase "Life is very distressing" on the low end, "Life is great" on the high end and "Life is so-so" in the middle. This measure has been used in several studies of individuals with disabilities from a variety of diagnoses ^{104, 113}. Please see [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.19.4 End Of Study Exit Interview

At the 1-year time point, study exit questions will focus on overall impact of the study as well as participants' activity between the end of intervention and the end of the study. Participants will also be asked to report the perceived value of the intervention. Please see [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.20 Secondary Outcome Measures: Comprehensive of Body Structure/Function, Activity and Participation

Comprehensive of all domains within the International Classification System.

6.3.20.1 Stroke Impact Scale (SIS)

See section 6.3.15.1 above for a description of the SIS.

6.3.21 Non-Outcome Monitoring

6.3.21.1 Physiologic Measures

Vitals including blood pressure and heart rate are taken at each evaluation and intervention visit. Physiologic measures are recorded on the respective evaluation or

daily intervention forms. Please see [section 2.S.2.11](#) of the MOP for the evaluation form (CRF).

6.3.21.2 Physical Exam

The physical Exam is a Screen measure and includes measures of vitals; goniometric measures of active and passive upper extremity range of motion; pain; spasticity using the Ashworth Scale; and mobility.

6.3.21.3 Immediate Post Intervention Exit Interview

Thirteen question survey Interview that will be administered after the end of the therapy phase. At the post-intervention assessment, participants will be asked a set of questions to provide manipulation checks or that address the extent to which critical components of interventions (e.g., interfering impairments, challenging workloads, participant chosen tasks, self-efficacy) were incorporated in the assigned intervention

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6.4 OFF-INTERVENTION REQUIREMENTS

There are no specific requirements for follow-up once Participants have completed the study intervention besides attending the post-intervention, 6 month post and 12 month post follow-up evaluations.

7 MANAGEMENT OF ADVERSE EXPERIENCES

The pre-screen and screen assessments serve to rule out medically unstable and/or at risk patients. Close physiologic monitoring by a licensed therapist will take place at all evaluations and intervention sessions. The assessments used in the proposed study are routine, clinical assessments of upper extremity motor movement used in physical and occupational therapy clinics and rehabilitation facilities.

The risks undertaken in this study are no greater than those in everyday physical or occupational therapy clinics where persons who have had a stroke are challenged daily to train, practice, exercise, and improve beyond their current abilities. The risks in undergoing upper extremity training are minimal and include:

1. experience of an elevated heart rate with exercise
2. temporary general fatigue
3. temporary muscle fatigue, and
4. muscle strains or sprains

Elevated heart rate is a normal response to exercise, especially in the acute phase of recovery. Risk for abnormal responses to exercise is greater in persons with hypertension or cardiovascular disease which is common for persons in this participant population. However, participation in exercise aids in reducing the hypertensive condition. The participants' response to exercise will be monitored routinely during all evaluations and training sessions. Mild to moderate fatigue is a normal response to increased activity and exercise. Fatigue will be monitored during all training sessions and will likely decrease as the exercise intensity and duration progress. As in usual rehabilitative care, should the participant experience any discomfort; exhibit exercise

responses beyond normal, expected values; or complain of fatigue; the exercise will cease and the problem addressed. No additional specific risks to the treatment groups of standard care and ASAP intervention are anticipated.

Additional specific risks to the experimental ASAP group may include feelings of anxiety and frustration, as well as feelings of accomplishment while the participants hand is in the mitt. The feelings of anxiety may be stressful; however, the participant will be monitored daily by project personnel to ensure safety. Previous work (EXCITE and BCAR studies) has revealed no adverse affects of the two weeks of restraint for the "good arm", since the mitt is removed at least during sleeping hours (6-8 hrs) and motion at the shoulder and elbow is not restricted during the restraint period. In this study, wearing of the mitt is on a voluntary basis. Prior to being given the mitt, the participant will receive extensive training during the orientation session. Included in the training is how to wear the mitt, when to wear the mitt, and above all, how to be safe while wearing the mitt. Emphasis is placed on the safety training with instruction on how to avoid risk for falls and to remove the mitt in risk situations. In case of emergencies or in situations where the participant may feel at risk of falling, the participant can and should remove the mitt.

Minimization of risk will be accomplished by monitoring vital signs with prescribed criteria for termination of the training session. Blood pressure (BP) and heart rate (HR) will be monitored prior to a session and at completion of each session. BP and HR must be within normal range for the participant prior to initiating each training session using the acceptable range given by the primary physician or the physician who conducted the medical screen. Additional criteria for termination include participant complaints of light-headedness, confusion, or dyspnea; onset of angina; excessive blood pressure changes (systolic BP greater than 200mm Hg, diastolic BP greater than 100 mm Hg), or drop in systolic BP greater than 20 mmHg and inappropriate bradycardia (drop in heart rate greater than 10 beats per minute). Should training be halted, the participant will be asked to rest while BP and HR are monitored and may resume only when BP and HR return to normal and prescribed values for the patient. If any of these conditions persist after rest, the participant's primary physician will be called and participant referred for evaluation. If the participant complains of angina at rest, loss of consciousness occurs, or cardiac arrest, emergency medical services through 911 will be called immediately. All evaluators and trainers will be CPR certified. Participant complaints of fatigue, dizziness, or discomfort will be immediately addressed, and if not resolved, training will cease for the day and participation will be re-evaluated. Physician consultation will be available throughout the study.

A data safety monitoring board (DSMB) will be established in collaboration with the NINDS to monitor the well being of the study participants, ensure scientific integrity of the study, and assure timely patient accrual. The physician at each site will also be responsible for reviewing the activities of the clinical trial including the incidence and type of adverse events. Each physician director will also consult with Dr. Carolee Winstein, PI of the trial, and/or Dr. Alex Dromerick, Principal Investigator and neurologist of the trial, relative to complications and a questionable progression of

participants. All serious adverse events will be reported immediately to the site physicians, as well as the IRB, and DSMB.

The University of Southern California has established definitions for adverse events, criteria for causally related and an adverse event protocol. These definitions and protocols will be used for reporting all adverse events from all sites for this study. Any adverse events at any and all study sites will be recorded and monitored as required by the USC Institutional Review Board and the USC Institutional Review Board and the Data Safety and Monitoring Board (DSMB). A report will be generated by the study site and submitted to the PI. The PI will submit a signed report to the USC IRB in compliance to their standard policies and procedures. The DSMB will provide on-going monitoring of adverse events for a pattern of events that would indicate increased risk or potential harm. This information could indicate a need to change the protocol or cease the trial. During the course of the study adverse events will be immediately entered into our data base, the data coordinating center will generate an adverse event report that will be sent to the Data Safety Monitoring Board, The USC Administrative Site, and all Site Investigators. As required by the USC protocol all serious events will be reported to the USC IRB within five days and they will also be reported to each local institutional review board as required. A cumulative adverse event-reporting table will be completed for annual continuing review.

If a participant experiences an injury that is directly caused by this study hospital expenses will have to be paid by the participant or the participant's insurance. No other compensation is offered.

8 CRITERIA FOR INTERVENTION DISCONTINUATION

Death: Official written confirmation. Resolution procedure: None, lost to intention to treat or to follow-up.

Relocation: Confirmation from caregiver/family member that participant is moving far enough away from site location as to preclude continued participation or availability for follow-up evaluations. Resolution procedure: Attempt to convince family to stay until end of intervention and to return for scheduled follow-up evaluations.

Hospitalization: Confirmation from caregiver/family member that participant has been hospitalized to the extent that ≥ 2 consecutive weeks of intervention will be lost or that follow-up evaluations cannot be undertaken within one month of scheduled date. Resolution procedure: None, lost to intention to treat or to follow-up.

Absence: Caused by prolonged illness, unanticipated travel, or loss of transportation to the extent that ≥ 2 consecutive weeks of intervention will be lost or that follow-up evaluations cannot be undertaken within one month of scheduled date. Resolution procedure: None, lost to intention to treat or to follow-up.

Non-compliance/conflict: The emergence of family conflict or combative interactions that preclude to attend therapy 5 days a week for the out-patient program, and attend follow-up sessions up to 12 months later. Resolution procedure: Attempt to work with family to assure compliance to behavioral contract and improved communication options.

Discovery of incorrect diagnosis: Caused by observations from re-read of neuroimages or other information provided subsequent to enrollment. Resolution procedure: None, lost to intention to treat or to follow-up.

9 STATISTICAL CONSIDERATIONS

9.1 GENERAL DESIGN ISSUES

9.1.1 Specific Aim 1 (Primary): Hypotheses

Primary Hypothesis for SA 1: At 1 yr post treatment, the time score from the Wolf Motor Function Test (WMFT) will be significantly smaller (faster) after ASAP than usual and customary occupational therapy care (DEUCC), controlled for dose.

Secondary Hypothesis for SA 1: At 1 yr post treatment, the proportion of patients with successful outcomes measured by the Stroke Impact Scale (SIS) hand domain and full SIS will be greater after ASAP than DEUCC, controlled for dose.

9.1.2 Specific Aim 2 (Secondary): Hypotheses

Hypothesis for SA 2A: At 1 yr post treatment, the proportion of patients with successful outcomes measured by the SIS hand and full SIS will be greater after ASAP than UCC, uncontrolled for dose.

Secondary Hypothesis for SA 2A: At 1 yr post treatment, the proportion of patients with successful outcomes measured by the Stroke Impact Scale (SIS) hand domain and full SIS will be greater after ASAP than DEUCC, controlled for dose.

Hypothesis for SA 2B: At 1 yr post treatment, the time score from the WMFT will be significantly smaller (faster) after DEUCC than UCC, uncontrolled for dose

Secondary Hypothesis for SA 2B: At 1 yr post treatment, the proportion of patients with successful outcomes measured by the SIS hand and full SIS will be greater after DEUCC than for UCC, uncontrolled for dose.

9.1.3 Study Design

The design is parallel groups. Each participant will be followed for a fixed follow-up period of 12 months post intervention. The one year follow-up is critical to assure that the changes induced by the intervention are persistent and meaningful in the patient's improved health status.

9.2 OUTCOMES

9.2.1 Primary Outcome

Wolf Motor Function Test (WMFT) -Time

The Wolf Motor Function Test (WMFT) ¹ determines the time required for patients with stroke to perform 15 everyday tasks with each upper extremity. Over the past 6 years, this measure has been used as either a primary or secondary outcome in at least 55 published studies. Performance time (up to 120 seconds), strength (in lbs for lifting and in kgs for hand grip), and quality of motor function based upon a 6 point scale Functional Activity Scale ⁸⁸ are assessed. Tasks are sequenced so that the first seven tasks involve simple limb movements, primarily of the proximal musculature; the next ten tasks require manipulation and distal control. Many of the tasks are modified from the Jebsen-Taylor hand function test ⁸⁹. Reliability for the Jebsen test was established by the original authors and grip strength reliability has also been reported by Mathiowetz

and colleagues⁹⁰. The reliability and validity of this test are: inter-rater reliability - correlation coefficient > .80 and validity, $\pm 3\%$ accuracy for the Jamar dynamometer⁹⁰. Each WMFT task is defined by a specific, detailed "anchoring" definition. For each task, information regarding patient positioning, placement of objects to be targeted or manipulated, distance of the participant to the object, whether seated or standing, and verbal instructions have all been operationalized.

9.2.2 Secondary Outcomes

A full battery of other measures will be taken at each evaluation point that will provide complimentary information about muscle strength, functional ability, depression, self-confidence, life satisfaction, reintegration, and subjective quality of life. The specific tests are detailed in the MOP, but listed here for completeness under the International Classification of Function and Disability Framework⁹¹. **Body Function/Body Structure:** Arm muscle torque⁹², WMFT strength items, UE Fugl-Meyer⁶⁰, depression (9-item self-report Patient Health Questionnaire-9)^{93, 94}, and 20-item Confidence in Arm and Hand Movements (CAHM). **Activity:** Stroke Impact Scale (SIS) hand items, WMFT strength items, Action Research Arm Test (ARA)⁹⁵, TEMPA^{96, 97}, and Motor Activity Log-MAL-28-QOM⁹⁸. **Participation:** Reintegration to Normal Living Index (RNLI)^{99, 100}, Satisfaction with Life Scale (SWLS)¹⁰¹⁻¹⁰³, Single Item Subjective Quality of Life (SQOL)^{104, 105}, and End of Study Exit Interview.

9.3 SAMPLE SIZE AND ACCRUAL

9.3.1 Sample Size And Power Calculations

We will recruit a total of 360 subjects, 120 randomized to ASAP, 120 to DEUCC, and 120 to UCC arms. The primary outcome is the change in log-transformed WMFT time score at 1yr from baseline. Our primary aim is to compare the changes in WMFT time score between ASAP and DEUCC groups. This is a pre-planned hypothesis and this hypothesis will be tested at a significance level of 0.05 at 1 yr follow-up. By a two-group 2-sided t-test and type I error of 0.05, the minimal effect size at 1 yr that can be detected with 80% power will be 0.40 for an attrition rate of 17%, and 0.42 for an attrition rate of 25%. This effect size is calculated as the difference in means in outcome variable between groups divided by common standard deviation of the outcome variable. Such standardized effect size is directly comparable among different studies. EXCITE trial showed that for the high functioning group, the average (+SD) change in the log-transformed WMFT in the intervention group was $-0.60 (+0.68)$ and in the delayed intervention group (control) it was $-0.28 (+0.61)$. The difference in the average change scores = -0.32 with pooled SD of 0.64, resulting in a treatment effect size of 0.50. For the low functioning group, the corresponding difference in average change scores was -0.57 (pooled SD of 0.9) between intervention and delayed intervention group, resulting in a treatment effect size of 0.63. For the small sample phase II VECTORS study, a similar analysis showed a difference in average change scores of 0.21 (pooled SD of 1.03) between high dose and control groups, resulting in a treatment effect size of 0.20. Our minimal effect size of 0.42 with 25% attrition rate is smaller than that for EXCITE and larger than that for VECTORS. As expected, the variance of the effect was higher for VECTORS (inpatient acute) than EXCITE (outpatient subacute). Effect size standardizes variances, thus it is comparable between

studies. Given the outpatient timing for I-CARE during a less dynamic period of change than VECTORS, we expect to have sufficient power to detect the effect size in WMFT. Our closely related secondary outcome measure is the success rate in SIS hand function, defined as the proportion of subjects with change ≥ 25 points out of 100 on the normalized SIS at 1yr. This 25 points change reflects a change of one-category on the 5-category scale in measuring hand function from full SIS. This self-report measure has face validity for clinical meaningfulness and corresponds well with our primary laboratory-based outcome of performance (i.e., WMFT). **Table 9.3.1** demonstrates the minimal success rate difference at 1 yr that can be detected with 80% power, 2-sided test and type I error of 0.05, using a chi-square statistic for a range of success rates expected in the control group. Thus, depending on the success rate in the DEUCC group, the minimal success rate difference that can be detected with 80% power ranges from 13.5% to 20% (17% attrition), and from 14.0% to 21% (25% attrition). Given the estimates for SIS hand function change from acute and post-acute control data described in Sec 4.3, we reasoned that if the DEUCC group success rate is greater than EXCITE, less than VECTORS, but comparable to that from the Kansas City sample, I-CARE is powered to detect a minimum of 21% difference between groups (see **Table 9.3.1**). A 21% increase in success rate for ASAP compared to an equivalent dose of usual and customary therapy is arguably a clinically significant effect. It is 4% lower than what was achieved for EXCITE and represents an NNT of 5, considered an efficacious treatment in the clinical trial literature^{114, 115}. We propose one interim data analysis for the primary outcome described in 5.10.a. One advantage of using O'Brien Fleming method is that the significance level at the end of the trial is approximately the same as that used for a single test. Thus, the 0.05 type I error used for the sample size and power consideration does not need to be adjusted. The comparisons between ASAP and UCC groups, and between DEUCC and UCC groups are secondary aims. The power to detect differences in WMFT and SIS7 success rates for these two secondary aims with type I error of 0.05 for each is the same as described above, that is, we have 80% power to detect a minimal effect size of 0.42 in WMFT with an attrition rate of 25%, and the minimal success rate differences in SIS hand function that can be detected with 80% power is the same as in **Table 9.3.1**.

Table 9.3.1 Sample Size Calculations

Table 9.3.1		
	Minimal success rate (difference) that can be detected with 80 % power in ASAP group	
Success rate in DEUCC	Assume 17 % attrition rate	Assume 25 % attrition rate
	N=100/group	N=90 /group
10 %	25.0 % (15.0 %)	26.0 % (16.0 %)
15 %	32.0 % (17.0 %)	33.0 % (18.0 %)
20 %	38.0 % (18.0 %)	39.0 % (19.0 %)
25 %	44.0 % (19.0 %)	45.0 % (20.0 %)
30 %	49.5 % (19.5 %)	50.5 % (20.5 %)
35 %	55.0 % (20.0 %)	56.0 % (21.0 %)
40 %	60.0 % (20.0 %)	61.0 % (21.0 %)
45 %	65.0 % (20.0 %)	66.0 % (21.0 %)
50 %	69.0 % (19.0 %)	70.5 % (20.5 %)
55 %	74.0 % (19.0 %)	75.0 % (20.0 %)
60 %	78.5 % (18.5 %)	79.5 % (19.5 %)
65 %	82.5 % (17.5 %)	83.5 % (18.5 %)
70 %	86.5 % (16.5 %)	87.5 % (17.5 %)
75 %	90.0 % (15.0 %)	91.0 % (16.0 %)
80 %	93.5 % (13.5 %)	94.0 % (14.0 %)

9.3.2 Participant Accrual

To achieve our goal to randomize 360 participants from 3 primary centers in 40_months (120/center, including 25% attrition), we believe that each center will be able to meet the following goals for the study enrollment period: Year 1: 6 months-18 participants (3/mo), Year 2: 36 participants (3/mo), Year 3: 36 participants (3/mo), Year 4: 10 months 30 participants (3/mo). We can administer the intervention at each clinical site to up to 3 persons in the same day because different clinicians are slated to provide each of the three treatment arms for the study. This capability will allow overlap of participants within a site and should account for recruitment and randomization fluctuations across centers.

Table 9.3.2: Participant Accrual

I-CARE Enrollment and Follow-up Timeline - Summary Across All Three Centers

Year 1 (April 2008 - March 2009) Totals Across All 3 Centers			
Total Enrollment:	54	Accumulated Enrollment thru Yr 1:	54
Total Intervention:	45	Accumulated Interventions thru Yr 1:	45
Total ASAP	15	Accumulated ASAP-r thru Yr 1:	15
Total DEUCC	15	Accumulated DEUCC thru Yr 1:	15
Total UCC	15	Accumulated UCC thru Yr 1:	15
Total Post Assessments:	45	Accumulated Post Assessments thru Yr 1:	45
Total Post 6 Month Follow-ups:	0	Accumulated 6-Mo Follow-ups thru Yr 1:	0
Total Post 12 Month Follow-ups:	0	Accumulated 12-Mo Follow-ups thru Yr 1:	0
Year 2 (April 2009 - March 2010) Totals Across All 3 Centers			
Total Enrollment:	108	Accumulated Enrollment thru Yr 2:	162
Total Intervention:	108	Accumulated Interventions thru Yr 2:	153
Total ASAP	36	Accumulated ASAP-r thru Yr 2:	51
Total DEUCC	36	Accumulated DEUCC thru Yr 2:	51
Total UCC	36	Accumulated UCC thru Yr 2:	51
Total Post Assessments:	108	Accumulated Post Assessments thru Yr 2:	153
Total Post 6 Month Follow-ups:	90	Accumulated 6-Mo Follow-ups thru Yr 2:	90
Total Post 12 Month Follow-ups:	45	Accumulated 12-Mo Follow-ups thru Yr 2:	45
Year 3 (April 2010 - March 2011) Totals Across All 3 Centers			
Total Enrollment:	108	Accumulated Enrollment thru Yr 3:	270
Total Intervention:	108	Accumulated Interventions thru Yr 3:	261
Total ASAP	36	Accumulated ASAP-r thru Yr 3:	87
Total DEUCC	36	Accumulated DEUCC thru Yr 3:	87
Total UCC	36	Accumulated UCC thru Yr 3:	87
Total Post Assessments:	108	Accumulated Post Assessments thru Yr 3:	261
Total Post 6 Month Follow-ups:	108	Accumulated 6-Mo Follow-ups thru Yr 3:	198
Total Post 12 Month Follow-ups:	108	Accumulated 12-Mo Follow-ups thru Yr 3:	153
Year 4 (April 2011 - March 2012) Totals Across All 3 Centers			
Total Enrollment:	90	Accumulated Enrollment thru Yr 4:	360
Total Intervention:	99	Accumulated Interventions thru Yr 4:	360
Total ASAP	33	Accumulated ASAP-r thru Yr 4:	120
Total DEUCC	33	Accumulated DEUCC thru Yr 4:	120
Total UCC	33	Accumulated UCC thru Yr 4:	120
Total Post Assessments:	99	Accumulated Post Assessments thru Yr 4:	360
Total Post 6 Month Follow-ups:	108	Accumulated 6-Mo Follow-ups thru Yr 4:	306
Total Post 12 Month Follow-ups:	108	Accumulated 12-Mo Follow-ups thru Yr 4:	261
Year 5 (April 2012 - March 2013) Totals Across All 3 Centers			
Total Enrollment:	0	Accumulated Enrollment thru Yr 5:	360
Total Intervention:	0	Accumulated Interventions thru Yr 5:	360
Total ASAP	0	Accumulated ASAP-r thru Yr 5:	120
Total DEUCC	0	Accumulated DEUCC thru Yr 5:	120
Total UCC	0	Accumulated UCC thru Yr 5:	120
Total Post Assessments:	0	Accumulated Post Assessments thru Yr 5:	360
Total Post 6 Month Follow-ups:	54	Accumulated 6-Mo Follow-ups thru Yr 5:	360
Total Post 12 Month Follow-ups:	99	Accumulated 12-Mo Follow-ups thru Yr 5:	360

9.3.3 Retention And Attrition

We recognize that there may be some *early* attrition once patients go home and consider an outpatient program such as I-CARE. We estimated 25% of eligible candidates would decline participation for reasons such as this. We revised our longer term follow-up attrition rate from 17% to 25% at 1 yr. From past experience it ranged between a low 12% to high 25%^{32, 33}. However, we do expect lower attrition than for EXCITE, because follow-up is shorter, intervention is not delayed, and all participants are eligible for at least usual therapy, if not study-related treatment. A number of activities found to be effective to optimize adherence and prevent loss to follow-up include but are not limited to, monthly phone contact, thank you notes, holiday and birthday cards, newsletters, certificates of completion, study t-shirts, pens, mugs etc. Further, taxi service will be provided when necessary from their local residence so that transportation does not become a barrier to participation.

9.4 DATA MONITORING

9.4.1 Data Safety Monitoring, Adverse Event Data Collection And Reporting

A data safety monitoring board will be established by the NINDS to monitor the well being of the study participants, ensure scientific integrity of the study and assure timely participant accrual. The Physician Investigators at each site will also be responsible for reviewing the activities of the clinical trial including the incidence and type of adverse events. Each site Physician Investigator will also consult with Dr. Dromerick, a board-certified Neurologist and Principal Investigator, relative to complications and questionable progression of participants during the intervention period. All serious adverse events will be reported immediately to the site physicians, as well as the IRB and DMC for study wide distribution. The University of Southern California has established the definition for an adverse event as “an undesirable and unintended result of therapy or other intervention” (Glossary <http://www.usc.edu/admin/provost/oprs/glossary/>). A detailed adverse event protocol in compliance with USC is outlined in the MOP.

9.4.2 Interim data Analysis

For ethical, scientific and economic considerations, we will perform one interim data analysis for the primary outcome time on the WMFT. This will occur when approximately half of the study sample in both ASAP and DEUCC groups have completed the trial. Only the primary outcome for the primary aim will be analyzed. We will use the O'Brien-Fleming group sequential method with the significance level defined as 0.005¹¹⁶ at the interim analysis to maintain the overall type I error of 0.05. Group assignment will remain blinded with codes A and B representing each group without revealing treatment. If the test of success rate in WMFT time at the interim analysis point reaches a p-value less than 0.005, DSMB will decide whether the trial should be stopped or whether analysis of secondary outcomes is necessary to provide additional support of the results. Otherwise the trial will continue to as planned. In addition, if interim analysis reveals a very small effect size, or participant recruitment is less than expected, conditional power will be computed to assess whether the trial should be continued. Conditional power is the power at the end of the trial given the current data with various assumptions of what might happen over the remaining trial period. The DSMB will

evaluate all the results and decide to continue or stop. The advantage of the O'Brien Fleming method is: 1) it is conservative for significance at the interim analysis point, and 2) it maintains the conventional p-value in the final analysis.

9.5 DATA ANALYSIS

We begin by characterizing the study sample using descriptive statistics to demonstrate the distribution of demographics and baseline characteristics. This will include mean, median, standard deviation and range for continuous variables and frequency for categorical variables. The distribution will be produced for the overall sample, and again for each randomized group, separately. Details are provided below of the comprehensive statistical data analysis plan for each hypothesis. For all analyses, assumptions required for the data distribution (e.g., normal distribution) will be checked. Any transformations of data or alternative methods necessary to analyze the data will be determined by examining the structure of the data. All analyses will be performed in accord with the intent-to-treat principle (ITT, i.e., group status will be determined by randomization at baseline). Although not expected, if subject compliance to the treatment protocol assigned is low, analyses will also be conducted based on actual treatment and dose received. Results from both analyses will be compared and any discrepancy reported. For subjects who miss evaluation visits, therefore with missing data, every effort will be made to collect the primary and some of the secondary outcomes. In our primary data analysis, we do not intend to impute any missing data, however, baseline characteristics between subjects who do and do not complete the trial will be compared. Any differences will impact generalization of the trial results. In addition, dropouts between randomized groups will be compared to assess any possibility of differential dropouts that might relate to treatment. We have incorporated a 25% dropout rate in our sample size estimation; this is on the high end of estimations based on our previous experience. Thus, we expect to have the power as we have planned. If missing data exceeds what we have anticipated, additional analysis will be conducted incorporating various existing missing data imputation methods. This includes: missing indicator, last-value-carry-forward, estimating the missing data using a regression approach and incorporating subject characteristics. Data that are missing completely at random (MCAR) will not create bias. Data that are missing at random (MAR, i.e., no new information can be gained in the missing data given the data that we measured for these subjects already) can create bias if not handled correctly. Under MAR, if the model assumed for the data is correct, estimates from likelihood-based data analysis approaches will be valid^{117, 118}. If missing data are not MCAR or MAR, obtaining valid estimates is more complicated, since one has to make assumptions about the distribution of missing data which cannot be fully tested (data not collected). We will perform a sensitivity analysis using various approaches. Consistency of results from all approaches will provide assurance of the trial results. Similarly, for non-compliance and dropouts, periodic investigator meetings, DSMB meetings and interim analysis will identify any problems early and appropriate actions will be taken to minimize any problems prior to trial end. Nonetheless, if non-compliance and/or dropouts are substantial in the final analysis, besides ITT and using actual treatment and dose received, we will perform a sensitivity analysis using other non-standard methods that have been proposed in the statistical literature. All methods have

underlying assumptions that are not testable, thus, sensitivity analysis is appropriate. Consistency of results from all approaches will provide assurance of the trial results. Any discrepancies will be investigated further.

9.5.1 Specific Aim 1-Analytic Plan

This aim compares ASAP to DEUCC group and is the pre-planned primary aim with the primary outcome defined as change in time score from the WMFT and the secondary outcome as the success rate from SIS hand function. The sample size is based on this aim with a type I error of 0.05, thus, a p-value of less than 0.05 will be used to declare significance. Baseline characteristics between ASAP and DEUCC groups will be compared first to assess whether randomization has achieved balance at baseline. Continuous variables will be compared using two-group t-test for normally distributed variables to test for mean differences and Wilcoxon rank sum test will be used for non-normally distributed variables to test for median differences. Chi-square or Fisher's exact test will be used for categorical variables to test for frequency differences. Characteristics that differ at baseline will be included as covariates in analyzing the primary and secondary outcomes. For primary outcome change in time score from WMFT at 1yr, a two-group t-test will be used to compare the mean change in log-transformed WMFT time score and analysis of covariance (ANCOVA) will be used to adjust for baseline variables that differ between groups and the stratified variables (center, initial motor impairment, time from onset to randomization). Adjusted least-square means and the associated 95% confidence interval will be presented as well as p-value. For the secondary outcome success rate in SIS hand function, success rate will be calculated as the percent of subjects in the ASAP and DEUCC groups that achieved a 25 point increase in normalized SIS hand function at 1 yr post treatment compared to baseline. The success rates in SIS hand function between groups will then be compared by logistic regression. The dependent variable is success (yes or no) and the independent variables are treatment group and covariates are baseline variables that differ between groups and the stratified variables. Adjusted rate ratio and the associated 95% confidence interval will be presented as well as p-value. Since there is no prior data or biological evidence suggesting that ASAP will have a differential effect on one subgroup compared to the other in the population we target, we do not plan to test for an interaction between treatment and any of the covariates in the main analysis. However, we will explore plausible interactions (see 9.5.3) through exploratory data analysis to generate hypotheses for future studies. For other secondary outcomes including WMFT functional ability score (FAS), strength, and full SIS, changes in normalized self-reported scores in strength, ADL/IADL, mobility, communication, emotion, memory and thinking, and participation at 1-yr post from baseline will be compared between ASAP and DEUCC groups using analysis of covariance. In addition, a composite physical domain, which includes strength, hand function, ADL/IADL, and mobility, will be created and compared in a similar way.

9.5.2 Specific Aim 2-Analytic Plan

This is the secondary aim. Aim 2A compares ASAP to UCC and Aim 2B compares DEUCC to UCC to assess a pure dose effect of usual therapy. The analytic approach is the same as that described for the primary aim (Sec 9.5.1) except ASAP will be

compared to UCC under Aim 2A and DEUCC will be compared to UCC under Aim 2B. Briefly, outcomes include WMFT time score and success rate for SIS hand domain and changes in full SIS domains at 1-yr post treatment from baseline. Logistic regression will be used to compare the success rate and ANCOVA will be used to compare changes in full SIS domain and WMFT between groups. Any baseline measures that differ at baseline and stratified baseline variables will be included as covariates.

9.5.3 Other Secondary And Exploratory Data Analysis Plans

For other secondary measures including those outlined in 5.8.3 and 5.8.4, we will take a similar approach as described above to assess differences between groups. In general, for dichotomous outcomes, logistic regression, and for continuous outcomes, ANCOVA will be used. Unbalanced baseline covariates and stratified variables will be included as covariates. For exploratory data analysis, possible interactions between treatment and baseline variables, such as high or low motor impairment groups, time from stroke onset to randomization, stroke types (ischemic vs. hemorrhagic), age and gender groups will be tested. If significant, the nature of the interaction will be further characterized by performing subgroup analyses. Baseline continuous variables will be categorized in order to allow a clinically meaningful presentation/interpretation. Cut-points will be defined by the overall distribution across the three groups. The results of these exploratory analyses will be used only to generate hypotheses for designing future confirmative studies. In addition, we will include immediate post treatment and 6-month follow-up analysis to assess overall time trend differences between groups. The outcome data will be plotted or graphed against time (baseline, immediate post intervention and 1-yr post intervention) to visually examine any patterns of change. These longitudinal data will be modeled using mixed-effects model to quantify and test for the overall treatment effect by testing for interaction between group and time and test for the pattern of treatment effect difference at different evaluation points by testing for a three way interaction among group, time and evaluation point. Intercept will be specified as a random effect. A significant three-way interaction suggests that treatment has different effects on the outcome during the trial. For example, treatment effect did not start until immediate post-treatment, or treatment effect plateaus after 6-month post treatment, etc. Once such different patterns are identified, further stratified analyses will be conducted to evaluate the nature of any treatment group differences. All analyses will consider appropriate baseline difference adjustments.

Finally, and corresponding to the International Classification for Disability and Functioning model⁹¹, with linkages between body function/structure, activity, and participation, we will examine the relationship between changes in upper extremity activity (WMFT) and self-reported hand function (SIS) using our primary and secondary outcomes. These exploratory analyses will compare the change in WMFT performance and several subdomains of the SIS including hand function, composite physical function, and social participation. To this end, path analysis methods will be implemented.

SAS (SAS Institute Inc, Cary, NC) will be the primary software used for all statistical analysis. We will use SAS PROC LOGISTIC for logistic regression, SAS PROC GLM

for ANCOVA, and SAS PROC MIXED and PROC NLMIXED for repeated measures longitudinal data analysis.

10 DATA COLLECTION, SITE MONITORING AND ADVERSE EXPERIENCE REPORTING

10.1 RECORDS TO BE KEPT

Participants' research records including all demographic information, contact information, assessment data and training data will be kept confidential by the investigators to the extent permitted by law. Specific study-related information may be sent to the sponsor, who is the National Institutes of Health, but the participants' names will be deleted.

Every effort will be made to keep the participants' personal information confidential. Personal-identifying data will be stored in locked files and in password-protected computer accounts to ensure confidentiality. Only staff that is processing these data for Institutional Review Board (IRB)-approved research studies will have access to the information. We cannot guarantee absolute confidentiality. Participants' personal information may be disclosed if required by law. The information from this study may be published in scientific journals or presented at scientific meetings, but the participants' identity will not be revealed.

If photographs, videos, or audiotape recordings of the participants will be used for educational purposes, the participants' identities will be kept confidential. The participants may review the tapes if they wish and obtain a copy if they would like. The research team will have access to these tapes for data analysis purposes. After the data analysis is complete, the tapes will be destroyed.

10.2 ROLE OF DATA MANAGEMENT

10.2.1 Clinical Site Responsibilities

Each clinical site will be responsible for all data collection and data management for the participants they recruit. Data management includes storage, security and confidentiality as discussed above, and data entry. Therefore, each site will enter the data using web based entry designed and managed by the Data Management Center at USC (see below for details).

10.2.2 The Data Management Center (DMC)

The Data Management Center (DMC) is housed at the Statistical Consulting and Research Center (SCRC), Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA.

The DMC responsibilities in data management include providing expertise for multi-center studies in all aspects pertaining to the development and operation of the randomization process, website and database design, data quality checking, study reports and data analysis. The DMC team includes a:

1. Director: provide guidance to Do-Director in all aspects pertaining to the development and operation of the DMC for I-CARE; participate in the steering

committee meetings; and participate in writing of the reports and manuscripts for I-CARE.

2. Co-director: participate in development and modification of study Manual of Procedures (MOP); advise the Principal Investigators and Steering Committee on statistical and design issues; review data quality; prepare data reports for study investigators; design and execute interim and final data analysis; prepare reports for the Data Safety Monitoring Board (DSMB); participate in the Steering Committee meetings; and participate in the final study report and manuscript writing.
3. Information Technology Supervisor/Statistician: the statistician will be responsible for developing the randomization list; preparing monthly reports summarizing recruitment (overall and by clinical site); generating visit reminders for the clinical sites; preparing biannual reports for the DSMB including a summary of demographic data, compliance and safety data; generating reports for study investigators as needed; developing programs for interim and final data analysis; and producing tables and graphs for data reporting, presentations and manuscript publication. This person is also responsible for maintaining the study server, updating software, and maintaining study computers.
4. Data Manager: work with the Bioinformaticist in building the data dictionary and web forms for the I-CARE dedicated web entry system and updating the data dictionary; be responsible for managing the I-CARE databases; developing quality control procedures to monitor the data overall and by center; producing internal quality control reports (such as missing data, missing visits, data outlier, etc.); communicating with the Clinical Site Coordinators to rectify data problems; working with the Co-Director and Statistician to retrieve appropriate data for reports and analysis; and travel to clinical sites to conduct data audits.
5. Bioinformaticist: development of a website for I-CARE trial, which will contain a public website with information on study objectives, news items, relevant literature, seminars/workshops, etc. The website will include a secure component for accessing the study MOP, IRB documents, data collection forms, the database with friendly data entry screens for clinical sites to input data directly, a data dictionary, recruitment reports, and data safety monitoring reports. Only authorized study personnel will have access to the secure website component. This person will also be responsible for maintaining and modifying the website and database by making necessary changes and updates throughout the study.

Please see [section 2.T](#) of the MOP for details regarding the DMC specific aims, roles and responsibilities.

10.3 QUALITY ASSURANCE

Data will be checked for integrity and verification. The remote data entry component will include online error checking, based on range checks or relational checks. To ensure quality data, pre-programmed range checks will be defined in the data dictionary and built into the web-based data entry system. An error report page (when errors occur) will be interactively returned to the user. Once corrections are completed, a 'verified screen' will appear and it will be the user's responsibility to verify that the data about to be submitted are correct, thereby offering the user an opportunity to make additional

corrections before submission. Variables defined as required will not allow blanks to be entered. Based on our past experience, a data element will not be collected unless it meets one of the following needs: study objective; confirm eligibility; government regulatory information; assessment of safety; quality assurance. By limiting the scope of data collected to essential elements, the net effect will be to have high quality data. One reason is that those responsible for collecting the data will have the necessary time to collect and check the most critical data elements. Security will be flexible enough to monitor access down to the data field level. The database will track who made the transaction and the time and date of the transaction for each successful data submission. Every successful submission of a transaction will be recorded in on-line archive tables, this providing a complete audit trail of data/form changes and/or modifications. That is, the database can be recreated to any point in time. The analytic computer will contain snapshots of the data at specific times, including a current copy. Remote users will not conduct any direct transactions on the analytic databases.

In addition to the database records, each site will keep all hard-copy records and Standardized Case Report Forms (CRFs) available for inspection by the Site PI. Standardized Case Report Forms will be provided for use at the investigational sites through download from the Manual of Procedures. Investigators are responsible for completion and timely submission of the data to the DMC for data processing. Quality assurance procedures are designed to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed, and that complications and adverse device effects are reported. Incoming data are reviewed to identify inconsistent or missing data and adverse effects. Data problems will be addressed in calls and/or emails to the investigational site and during site visits by the Executive committee member. All hard copy forms and electronic data files will be secured to ensure confidentiality.

10.4 ADVERSE EXPERIENCE REPORTING

A data safety monitoring board will be established by the NINDS to monitor the well being of the study participants, ensure scientific integrity of the study and assure timely participant accrual. The Physician Investigators at each site will also be responsible for reviewing the activities of the clinical trial including the incidence and type of adverse events. Each Physician Investigator will also consult with Dr. Alex Dromerick, a board-certified Neurologist and Principal Investigator of the trial, relative to complications and questionable progression of participants during the intervention period.

All serious adverse events will be reported immediately to the site physicians, as well as the IRB and DMC for study wide distribution. The University of Southern California has established definitions for adverse events, criteria for causal relationships, and an adverse event protocol. These definitions and protocols will be used for reporting all adverse events from all sites for this study ([section 2.P](#) of the MOP). During the course of the study adverse events will be immediately entered into our data base, the DMC will generate an adverse event report that will be sent to the Data Safety Monitoring Board, the USC Administrative Site, and all site investigators. As required by the USC protocol, all serious events that are related or possibly related and unexpected will be

reported to the USC IRB within five days if and they will also be reported to each local IRB as required. A cumulative adverse event reporting table will be completed for annual continuing review.

The DMC statistical core will check the data monthly for data safety monitoring variables that may lead to a 'stop' of the study. Every six months, we will prepare an institutional performance monitoring report, part of which will be on data timeliness, accuracy, and completeness scores. We will also give projections for each site of the scheduled completion dates for accrual, based on the actual accrual. In addition to the monthly data monitoring reports, participant accrual will be monitored weekly by site using a graphical plot of actual vs. planned accrual along with an accumulated enrollment by month for each site. These reports will be sent by email first to the Project Manager for verification, and once verified, sent out to all sites and posted on the secure reports page of the I-CARE web site. We have found this procedure to be very effective in helping to meet expected participant accrual for our clinical research network, PTClinResNet and plan to use a similar procedure for I-CARE. Please see [section 2.P.2](#) of the MOP for details regarding adverse event reporting.

11 HUMAN SUBJECTS

11.1 INSTITUTIONAL REVIEW BOARD (IRB) REVIEW AND INFORMED CONSENT

This protocol and the informed consent document ([section 2.I](#) of the MOP) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed screen informed consent form will be obtained from the participant to determine eligibility. If the potential participant is a candidate, they will be asked to sign a Main Study Informed Consent that will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Potential participants are given ample opportunity to ask questions about the study. Participants who cannot consent for themselves are excluded from participation in this study. A copy of the consent form will be given to the participant or legal guardian/caretaker, and this fact will be documented in the participant's record.

11.2 PARTICIPANT CONFIDENTIALITY

Participant confidentiality will be maintained with all data records noting a code number and will be stored in a locked cabinet in the laboratory. All data will be password protected. Any evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain participant confidentiality. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee.

11.3 STUDY MODIFICATION/DISCONTINUATION

The study may be modified or discontinued at any time by the IRB, the NINDS, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NINDS prior to submission.

13 REFERENCES

Please refer to the end of the Manual of Procedures (MOP) for a complete listing of all [references](#).

2.A PROTOCOL

2.A PROTOCOL

Title:

Interdisciplinary Comprehensive Arm Rehab Evaluation (ICARE) Stroke Initiative: A prospective, randomized, single-blind, multi-site, three arm clinical trial of upper extremity rehabilitation in 360 adults between 14 and 106 days post-acute stroke

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Supported by:

The National Institute of Neurological Disorders and Stroke (NINDS)
1 UO1 NS056256

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PRÉCIS

Study Title

Interdisciplinary Comprehensive Arm Rehab Evaluation (ICARE) Stroke Initiative

Objectives

Our proposed objective is to randomize 360 participants into a phase III, multi-center (7 sites), single-blind RCT and investigate the effectiveness of a focused, intense, evidence-based, upper extremity rehabilitation program (Accelerated Skill Acquisition Program, ASAP), administered during the early post-acute outpatient interval, and to compare the effects of ASAP to that of an equivalent dose of usual and customary outpatient therapy (dose equivalent usual and customary care, DEUCC) on upper extremity functional recovery 1 year after randomization. Our ultimate goal is to provide evidence to optimize post-stroke rehabilitation practice for those with mild to moderate upper limb impairments and reduce disability in the broadest sense.

Design and Outcomes

The ICARE Stroke Initiative is a 5-year, phase III, single-blind, multi-center (7 clinical sites) RCT to compare Accelerated Skill Acquisition Program (ASAP), to a dose-equivalent (DEUCC) control group and an observational (monitoring only) control group (usual and customary care, UCC). We will recruit 360 adults, within 106 days of stroke onset, with mild to moderate upper extremity impairment.

Our primary outcome is the Wolf Motor Function Test (WMFT, time component). The Wolf Motor Function Test (WMFT)¹ determines the time required for patients with stroke to perform 15 standardized tasks with each upper extremity. Over the past 6 years, this measure has been used as either a primary or secondary outcome in at least 55 published studies. Tasks are sequenced so that the first seven tasks involve simple limb movements, primarily of the proximal musculature; the next ten tasks require manipulation and distal control. Each WMFT task is defined by a specific, detailed "anchoring" definition. For each task, information regarding patient positioning, placement of objects to be targeted or manipulated, distance of the participant to the object, whether seated or standing, and verbal instructions have all been operationalized.

Secondary outcome measures are listed here for completeness under the International Classification of Function and Disability Framework.

Body Structure/ Body Function: National Institutes of Health Stroke Scale (NIHSS), Arm Muscle Torque Test; WMFT (strength items); UE Fugl-Meyer (Motor); Patient Health Questionnaire-9 (PHQ-9); AsTex Sensory Index; 20-item Confidence in Arm and Hand Movements (CAHM), and a Cognitive battery of (5) assessments to include: Short Blessed Memory Orientation Concentration Test, D-KEFS Verbal Fluency Test, Hopkins Verbal Learning Test (HVLN-R), Color Trails Tests 1 & 2 and Digits Span Backward
Activity: Stroke Impact Scale (SIS), WMFT (functional ability scale), and Motor Activity Log-MAL-28 (QOM).

Participation: Reintegration to Normal Living Index (RNLI), Satisfaction with Life Scale (SWLS), Single Item Subjective Quality of Life (SQOL), and Exit Interview.

Comprehensive Body Structure/Function, Activity and Participation: Stroke Impact Scale (SIS), EQ-5D, Functional Independence Measure (FIM).

Non-Outcome Monitoring: Physiologic measures, Physical exam, and Immediate Post Intervention Interview, and Monthly Telephonic Interviews and Study Exit Interview.

Accelerated Skill Acquisition Program (ASAP) Intervention: The ASAP program begins with an orientation session. Training sessions are 3x per week for 10 weeks for a total of 30 hours, with rest breaks as needed, but kept to a minimum. The training intervention is based on the fundamental elements of skill acquisition through task-specific practice, impairment mitigation to increase capacity, and motivational enhancements to build self-confidence. Eight principles are used to guide ASAP intervention sessions: 1) Ensure challenging and meaningful practice, 2) address important mutable impairments, 3) enhance motor capacity through overload and specificity, 4) preserve natural goal-directedness in movement organization, 5) avoid artificial task breakdown when engaging in task-specific practice, 6) active patient involvement and opportunities for self-direction are feasible and desirable, 7) balance immediate and future needs for efficient motor skill and capacity enhancement with the development of confidence and self-management skills, and 8) drive task-specific self-confidence (self-efficacy) high through performance accomplishments.

Dose-Equivalent Usual and Customary Therapy (DEUCC) Intervention: Participants that are randomized to this group will be treated by a licensed and experienced occupational therapist working in the outpatient setting. The therapists are free to design and implement treatment according to their usual practice. We will require access to the treatment record, from which the project personnel will obtain minimal documentation and monitor treatment throughout the 30 hours of treatment. The number of treatment hours is constrained to 30 for equivalency with the ASAP therapy dose. The clinical site coordinator will inform the treating therapist of this stipulation only after the prescriptive dose has been determined and documented.

Usual and Customary Care Therapy (UCC) Intervention: Participants that are randomized to UCC will be treated by a licensed and experienced occupational therapist working in the outpatient setting. The therapists are free to design and implement treatment according to their usual practice. We will require access to the treatment record, from which the project personnel will obtain minimal documentation and monitor treatment throughout the UCC interval. This is an observation only group with no a priori stipulation of the number of visits. Documentation will be the same for UCC and DEUCC.

Duration: Time on study for all participants includes the intervention time, no greater than 16 weeks post-randomization, with randomization occurring between 14 and 106 days post-stroke, and an additional 12 months post-randomization for follow-up. The schedule is as follows:

1. Pre-Screening (Express Chart Screen) of non-modifiable demographics to determine eligibility;
2. Screening Evaluation to determine eligibility, which includes: Brief Clinical Screen (BCS), Detailed Clinical Screen (DCS), Brief Medical Exam, Baseline Evaluation;
3. Randomization to group; (14-106 days post-stroke)
4. Intervention (10-16 weeks post-randomization);
5. Immediate Post-Intervention Evaluation (16-20 weeks post-randomization);
6. 6-month Post Randomization Evaluation (and
7. 12 month Post-Randomization Evaluation.

Sample Size and Population

We will recruit a total of 360 participants within 106 days post-stroke onset with mild to moderate upper extremity impairment. All persons with a known stroke diagnosis that are admitted to the 7 rehabilitation sites or their affiliated sites (including but not limited to: satellite sites, acute medical units, outpatient rehabilitation units, outpatient medical groups) and any

direct referrals will be pre-screened for inclusion in the trial. All persons meeting eligibility criteria will be afforded the opportunity to participate in the trial. Women greater than or equal to 21 years of age and members of minority groups and their subpopulations will be included in this trial.

1 STUDY OBJECTIVES

1.1 PRIMARY OBJECTIVE

This RCT has one primary aim:

Specific Aim 1 (Primary): To compare the efficacy of a fully-defined, evidence-based and theoretically defensible therapy program (ASAP) and an equivalent dose of usual and customary therapy initiated within the earliest post-acute outpatient interval (14-106 days post stroke) for significant gains in the primary outcome of paretic upper extremity function 1 year after randomization.

Primary Hypothesis for SA 1: At 1 yr post randomization, the time score from the Wolf Motor Function Test (WMFT) will be significantly smaller (faster) after ASAP than usual and customary therapy (DEUCC), controlled for dose.

Secondary Hypothesis for SA 1: At 1 yr post randomization, the proportion of patients with successful outcomes measured by the Stroke Impact Scale (SIS) hand domain and full SIS will be greater after ASAP than DEUCC, controlled for dose.

1.2 SECONDARY OBJECTIVES

Specific Aim 2A (Secondary): To compare the efficacy of a fully-defined, evidence-based and theoretically defensible therapy program (ASAP) to that of an observation only usual and customary (UCC) therapy program initiated within the earliest post-acute outpatient interval (14-106 days post stroke) for significant gains in the primary outcome of paretic upper extremity function 1-yr after randomization.

Hypothesis for SA 2: At 1 yr post randomization, the time score from the WMFT will be significantly smaller (faster) after ASAP than UCC, uncontrolled for dose.

Secondary Hypothesis for SA 2A: At 1 yr post randomization, the proportion of patients with successful outcomes measured by the SIS hand and full SIS will be greater after ASAP than UCC, uncontrolled for dose.

Specific Aim 2B: To compare the efficacy of one dose-equivalent usual and customary outpatient therapy program (DEUCC) to an observation only, usual and customary outpatient therapy (UCC) program initiated within the earliest post-acute outpatient interval (14-106 days post stroke) for significant gains in the primary outcome of paretic upper extremity function 1 yr after randomization.

Hypothesis for SA 2B: At 1 yr post randomization, the time score from the WMFT will be significantly smaller (faster) after DEUCC than UCC, uncontrolled for dose.

Secondary Hypothesis for SA 2B: At 1 yr post randomization, the proportion of patients with successful outcomes measured by the SIS hand domain and full SIS will be greater after DEUCC than for UCC, uncontrolled for dose.

This RCT will provide the critical foundation for at least four planned complementary studies designed to explore underlying mechanisms within subsets of the recruited

patient sample. These include: neuroimaging, genotyping, TMS and cost effectiveness studies currently under development.

2 BACKGROUND

2.1 RATIONALE

An assessment of current therapy practices during the post-acute period of outpatient rehabilitation and the state of phase II and III evidence has led to the development and re-design of this RCT proposal. Of the 700,000 individuals who experience a new or recurrent stroke each year, a majority have considerable residual disability²⁻⁷. Sixty-five percent of patients at 6 months are unable to incorporate the paretic hand effectively into daily activities^{5, 6}. In turn, this degree of functional deficit contributes to a reduced quality of life after stroke^{3, 6, 8, 9}. The extent of disability has been underplayed by the use of the Barthel Index¹⁰ that captures only basic activities of daily living such as self-care and does not extend to activities and participation at higher levels of functioning that are most affected by a residual upper extremity disability^{6, 11-14}. The past decade has witnessed an explosion of different therapy interventions designed to capitalize on the brain's inherent capability to rewire and learn well into old age and more importantly for rehabilitation, after injury. The most effective arm-focused interventions with the strongest evidence and potentially the most immediate and cost-effective appeal for the current health-care environment share a common emphasis on focused task-specific training applied with an intensity higher than usual care^{15, 16}. Therefore, our primary aim is to compare the efficacy of a fully defined, hybrid combination of the most effective interventions (forced-use/constraint-induced therapy and skill-based/impairment-mitigating motor learning training), the Accelerated Skill Acquisition Program (ASAP), to an equivalent dose of usual and customary outpatient therapy.

Although the exact proportion of stroke survivors who are mildly to moderately impaired is not known, conservative estimates range between 5% and 30%. These are individuals who return to the community but with significant disablement¹⁷. The paucity of dose-equivalent designs in the stroke upper extremity clinical trial literature and including our recent EXCITE trial¹⁸, highlights the necessity and importance of this phase III RCT evidence^{19, 20}. Unlike EXCITE, our intervention targets the immediate post-acute period, in large part because this timing is considered optimal for several important reasons: 1) it enables a supportive interaction between processes associated with experience-dependent and injury-induced cortical reorganization that are known to influence functional recovery^{21, 22}, 2) it may attenuate the detrimental effects of maladaptive compensatory strategies (e.g., learned non-use) currently promoted during inpatient rehabilitation⁵, that may with time be reinforced and become more difficult for the patient and clinician to reverse²³, 3) it is not too early as to be overly aggressive during a more vulnerable period both physiologically and psychologically^{21, 24}, and 4) it is simply not practical to introduce a distributed, 30-hr, upper extremity task-specific training program into an already dwindling acute inpatient length of stay^{5, 19}. Indeed, recently, Lang and colleagues showed that affected UE use is minimal during the inpatient rehab stay in patients with mild to moderate acute hemiparesis²⁵.

The following section describes the scientific and practical rationale for ASAP parameters including therapeutic dose and duration. Next, we describe the conceptual framework and how evidence from three domains of skill, capacity, and motivation integrate, inform and support the ASAP protocol. Finally, we describe the significance of this trial with respect to its potential impact on current practice for stroke rehabilitation.

2.1.1 RATIONALE FOR PARAMETERS

2.1.1.1 Why Apply The Intervention 14 To 106 Days Post-Stroke?

The recent ASA/AHS endorsed Clinical Practice Guidelines²⁶ review evidence for therapy intensity and duration. While the heterogeneity of the studies combined with borderline results in many trials limits the specificity and strength of any conclusions overall, the trials support the general concept that rehabilitation can improve functional outcomes, particularly in patients with lesser degrees of impairment. There is weak evidence for a dose-response relationship between intensity of the rehabilitation intervention and functional outcomes. For example Sterr and colleagues demonstrated that while both groups improved, 6 hrs of CIT led to greater improvements at 1 month on the WMFT and MAL than 3 hours delivered daily, over a two-week period in 15 adults with chronic hemiparesis²⁷. Despite limitations of these individual studies, the conclusions among several systematic reviews are fairly consistent: Two meta-analyses both concluded that greater intensity produces slightly better outcomes^{28, 29}. Kwakkel²⁹ reported a small but statistically significant intensity effect relationship in the rehabilitation of stroke patients. The literature specific to upper extremity treatment is mixed. Other than EXCITE, there are no multi-center trials in the literature. A recent two-center observer-blinded, stratified, block-randomized controlled trial with 91 patients (47 experimental, 44 control) within 1 yr of stroke who participated in three 90 min sessions/week for 6 weeks of task-oriented training for upper extremity did not improve voluntary movement or manual dexterity of the affected arm³⁰. These results were not surprising when considering the heterogeneous sample that was selected on walking impairment, and not arm impairment; in fact, 16% of the patients had no distal (wrist/fingers) movement capability. If no hand dexterity is apparent by 6 weeks after stroke the likelihood of achieving hand function at 6 months is poor³¹. This study highlights the need for well-designed investigations with inclusion criteria that are matched to the specific intervention, in this case, that requires active motor participation.

2.1.1.2 What Is A Therapeutic Dose Of Task-Specific Training: Why 30 hours for the Therapy Intervention?

For ICARE, we chose a distributed schedule of 30 hrs of training for scientific and pragmatic reasons. We re-designed ICARE to include a comparison control group, an observation only, usual and customary (UCC) outpatient occupational therapy. We expect considerable variation in the UCC dose both by site and across the 5-year monitoring period. These observation data will be important in the end from a policy standpoint and should be useful to estimate the cost if more prescriptive practice guidelines were to be implemented, especially if it can be shown to produce better outcomes. Pilot data from our multi-site outpatient survey suggests that 30 hrs

distributed over 4-10 weeks would be somewhat higher than that commonly prescribed, but still practical in that it would allow patients to participate in other concurrent therapy services (e.g., physical therapy and speech therapy). Thirty hours is 33% more than what we used in our single site phase II trial that commenced during inpatient and extending to outpatient (20 hrs distributed over 4-6 weeks)³²; it is 50% of that used for EXCITE (60 hrs over 2 weeks) during the 3-9 month post outpatient period³³; twice that used by Page³⁴ (15 hrs over 10 weeks, 30 min sessions, 3x/week) in a recent phase I acute trial of mCIT, and 55% of that prescribed in the recent home-based RCT of a multifaceted therapeutic exercise program (54 hrs over 12 weeks) in subacute stroke³⁵. *Therefore the 30 hr dose is well within the range of previous intervention trials shown to be effective, it is practical for the outpatient environment, yet it is likely higher than the usual average dose that is prescribed for this patient group.*

2.1.1.3 Why A 10 Week Duration?

This represents a departure from the 'massed practice' philosophy of the signature CIT protocol and the one we used in EXCITE, and in fact is closer to that prescribed in more recent reports that have used a modified CIT and distributed protocol of practice^{34, 36-43}. Together, there is considerable evidence for efficacy of task-specific practice using these more distributed training schedules in upper extremity Neurorehabilitation^{15, 44}. Although there are no direct comparisons (massed vs. distributed) in neurorehabilitation, there is a long history of this debate for motor learning⁴⁵. The term 'massed' practice is defined as a set of practice trials in which the performance-rest ratio is high and the proportion of rest between practice attempts is relatively shorter than the amount of time spent practicing. In contrast, 'distributed' practice refers to a set of practice trials in which the performance-rest ratio is low and the rest time between trials is longer than the amount of time spent practicing⁴⁶. Several reviews of the massed vs. distributed practice schedule for motor learning have concluded that the effects of the various performance and rest schedules seem to be different for discrete and continuous tasks. For discrete tasks, such as tossing a ball or fastening a button, reducing the rest time (i.e., massed practice) has little or no influence on learning, and in some cases less rest may even be beneficial. However, for continuous tasks, such as handwriting, fatigue-like states are more apt to build up within a performance bout, suggesting that massed practice would be undesirable. Therefore, the majority of laboratory findings would support this notion—less rest between performance epochs degrades performance and has an overall detrimental effect on learning⁴⁷. Finally, such a distributed schedule is attractive from a practical perspective both to the patient and clinic; clinics consider a therapy visit to be ~ 45 min to an hour and usual and customary OT for stroke ranges from 2-3x/week for up to 10 weeks. Therefore the DEUCC arm could be implemented 3 visits/wk over 10 weeks without major disruptions to the standard operating procedures of the majority of outpatient clinics. *Together, the evidence from recent mCIT studies, the scientific evidence from motor learning, and practical considerations, support the distributed schedule of task-specific training chosen for ICARE.*

2.1.1.4 Why Include Mild To Moderate Stroke Severity?

Collectively, these observations suggest that the highest potential to overcome upper extremity impairment and improve upper extremity function is seen among patients who might be classified as “mild to moderately” impaired. These findings might apply to approximately 30%²³ of patients who have sustained a stroke and is supported by others^{31, 35}. Such considerations are important especially in harnessing functional potential during the first few months following stroke. In this context, it is prudent to recall that reduced lengths of stay and limited resources for subsequent subacute care have resulted in focused treatment toward compensatory behavior training, thus further limiting potentially beneficial voluntary activation of the impaired limb. This approach has become dictated by imposed constraints in treatment time and may be contributing to a learned non-use. A recent evidence-based clinical practice case report for the *New England Journal of Medicine*, suggested that the strategies for therapy after hemiplegic stroke during weeks 2-6 of inpatient rehabilitation include “training in compensatory techniques” such as training in one-handed dressing, bathing, and using the toilet⁵. In summary, for ICARE, we chose to target those patients with mild to moderate upper-extremity severity because this group is affected severely enough that they will not recover spontaneously, yet not so severely that they cannot participate in a systematic, focused and relatively intense and evidence-based task-specific training program. Our inclusion criteria are not as restrictive as those used in the EXCITE trial and therefore we expect to capture a larger percentage of those with upper-extremity impairments for ICARE than we did for EXCITE.

There are no known potential risks of the interventions.

2.1.2 SIGNIFICANCE OF THIS STUDY

Of the estimated persons with new stroke each year in the United States, 25-50% of stroke survivors experience persistent disability leading to partial or total dependence in activities of daily living. More effective treatment would lessen the disability, caregiver burden, and economic impact of stroke. Some prognostic figures suggest 65% of stroke survivors experience significant residual disability related to the upper extremity at 6 months⁶; the GAIN Americas trial estimated 38% had significant residual UE disability at 3 months. Using our EXCITE trial experience, we estimate that a total of 1689 of the 3404 screened EXCITE candidates, excluding those actually enrolled, would have met ICARE inclusion criteria. By centering our protocol on the shared focus of CIT and ASAP in task-specific training, bringing forward unique evidence-based attributes of one (e.g., impairment mitigation, bilateral training, active patient problem-solving through motivational enhancements), and reconciling theoretically distinct features (e.g., forced versus informed patient choice in the use of the mitt) in this revised plan, we eliminate the unnecessary comparison between two overlapping approaches and directly ask a more significant question that has implications for the practice of stroke rehabilitation. Specifically, is an equivalent dose (30 hrs) of a fully developed and standardized application of ASAP better for long-term functional arm and hand use than that achieved with usual and customary care delivered over the same duration (10 weeks) and beginning within the post-acute (14-106 days) period? If our

primary hypothesis is supported, the findings of ICARE could change current practice patterns during post-acute outpatient therapy for those with mild to moderate baseline impairments; even if our primary hypothesis is not supported, our secondary aim to compare the effects of DEUCC to that of UCC has relevance for determining if dose alone matters for functional outcomes. If our dose hypothesis is supported, the findings of ICARE could establish recommendations for the number of outpatient visits necessary to achieve clinically meaningful outcomes and for which no guidelines currently exist. Further, current and future experimental interventions such as pharmacological agents, gene therapy, stem cell implants, and direct cortical stimulation inevitably will be combined with optimal standardized and effective neurorehabilitation protocols to organize neuroplastic effects and maximize benefits. Finally, the ICARE initiative is aligned with the 2006 Report of the NINDS Stroke_Progress Review Group's established priorities for stroke recovery and rehabilitation research. Specifically, "to promote RCT's of important parameters of conventional rehabilitation interventions including: 1) Timing, dosing schedule...and 2) differential effects of various training paradigms.." ultimately to "develop science to maximize benefits of rehabilitation training and minimize adverse events".

2.2 SUPPORTING DATA

2.2.1 Study # 1: Extremity-Constraint Induced Therapy Evaluation, EXCITE
(Wolf PI-HDR01 37606, EXCITE){Wolf, 2006 #3414}

Context: Single site studies suggest that a 2-week program of Constraint Induced Movement therapy (CIMT) for patients more than 1 year after stroke and who maintain some hand and wrist movement can improve upper extremity function that persists for at least one year. **Objective:** To compare the effects of a multi-site, 2-week program of CIMT vs. usual and customary care on improvement in upper extremity function among patients 3-9 months post-stroke. **Design:** Prospective single-blind randomized multi-site clinical trial conducted at seven United States academic institutions between January 2001-03. **Participants:** 222 individuals with predominantly ischemic strokes.

Interventions: Participants were assigned to receive either CIMT (n = 106) (wearing a restraining mitt on the less affected hand while engaging in repetitive task practice and behavioral shaping with the hemiplegic hand) or usual and customary care n = 116) (ranging from no treatment after concluding formal rehabilitation to pharmacological or physiotherapeutic interventions) and were stratified by gender, pre-stroke dominant side, side of stroke, and level of paretic arm function. **Main Outcome Measures:** The Wolf Motor Function Test (WMFT), a measure of laboratory time and strength-based ability and quality of movement (functional ability), and the Motor Activity Log (MAL), a measure of how well and how often 30 common, daily activities are performed. Results: At 12 months, the CIMT group showed greater improvements than the control group on both the WMFT. Performance Time (19.3 s pre, 9.3 s 12 mo-52% reduction vs. 24.0 s pre, 17.7 s 12 mo-26% reduction in average time) between group difference, 34% 95% CI (12% - 51%), p < .001. and the MAL Amount of Use (1.21 pre, 2.13 12 mo vs. 1.15 pre, 1.65 12 mo) between group difference, 0.43 95% CI (.05 - .80), p < .001 and Quality of Movement (1.26 pre, 2.23 12 mo vs. 1.18 pre, 1.66 12 mo) between group difference, .48 95% CI (.13 - .84), p < .001. The CIMT group achieved a decrease of

19.5 in self-perceived hand function difficulty (SIS hand domain) vs. a decrease of 10.1 for the control group, between group difference, 9.42 (.27 - 18.57), $p < .05$.

Conclusions: Among patients who have sustained a stroke within the previous 3-9 months, CIMT produced statistically significant and clinically relevant improvements in arm motor function that persisted for at least one year and were not significantly modified by age, gender, or initial level of paretic arm function. *These findings suggest that further research exploring central nervous system changes that accompany the observed motor gains and research on alternate models of CIMT delivery are warranted.* As of August, 2007, 21 papers supported by the EXCITE grant have been published; 7 are in press, accepted for publication or in review; and an additional 23 are in various stages of preparation, including: 1) Persistence among improved outcome measures and 2) Impact of CI therapy: Comparison between 3-9 months or 1 year later. The content of papers in preparation is diverse including all aspects of the EXCITE Trial (methodological considerations, outcome papers, importance of intensity of training, health-related QOL, etc).

2.2.1.1 EXCITE EXIT INTERVIEW

An Exit-Interview instrument was completed at the 24-month assessment (end of study) by a subset of 73 participants from 5 participating EXCITE sites. In addition to the 20-item self-efficacy measure, Confidence in Arm and Hand Movements (CAHM), the instrument addressed participants' perspectives on the CIT intervention and EXCITE study participation. Participants rated the helpfulness of the mitt worn during the intervention as a mean of 5.51 (SD = 1.62), on a 7 point scale in which 1 = not helpful at all and 7 = very helpful. Thirty percent of the respondents perceived the mitt as not helpful at all to somewhat helpful, while the remaining 70% felt the mitt was more than somewhat helpful to very helpful. Perceived helpfulness was moderately correlated with SIS hand function at 24 months, $r = .417$, $p < .0001$. Thirty-five subjects had their dominant hand affected. Of these, 37% reported regaining the use of their hand to write, while 20% reported regaining the use of their hand to carry a heavy object. Subjects who regained the use of their dominant hand for writing rated the helpfulness of the mitt significantly higher (mean = 6.15, SD = 1.28) than those who did not regain hand use for writing (mean = 5.00, SD = 1.80), $t(33) = 2.02$, $p = .051$. No differences in perceived mitt helpfulness were noted in those who did or did not regain heavy object carrying capacity. It can be noted that the battery of tasks used in CIT training tends to favor dexterity rather than strength, and certainly unimanual as opposed to bimanual tasks, given the extensive mitt use. In an open-ended format, exit interview respondents were asked to indicate activities that they had wanted to do before CIT intervention that they still could not do. In addition to tasks involving dexterity in the affected hand (e.g., picking up small objects, using tools, and writing), responses included tasks involving both hands acting interdependently (e.g., cutting and peeling vegetables, buttoning shirts, playing golf or musical instruments) as well as in parallel (e.g., holding a book, carrying large or heavy objects, carrying hot objects).

Relevant to ICARE, these findings suggest that: 1) participants generally found the mitt helpful in encouraging affected hand use, though a minority did not, 2) there are a

substantial number of bimanual tasks that these individuals would like to regain, and 3) consistent with a Rasch analysis of SIS hand function items³, tasks requiring muscle strength are particularly difficult for individuals after stroke⁴⁸. Finally, the EXCITE persistence analysis showed improved SIS domains at 16 and 24 months in the immediate group. *These findings support decisions about ASAP to: 1) encourage mitt use in collaborative planning, especially when tasks involve dexterity or fine motor control, 2) require that at least one preferred task involve bimanual activity, and 3) incorporate capacity building for strength-requiring tasks (e.g., lifting grocery bag), in addition to those that challenge fine motor control and dexterity.*

2.2.2 STUDY # 2, SECONDARY OUTCOME MEASURE: SIS HAND DOMAIN From EXCITE And Other Data Sets Closer To The ICARE Post-Acute Period

Background: The SIS is a well-established health status measure with reliability and validity^{17, 49} and in each of the eight domains. Duncan and colleagues report that at baseline the SIS had acceptable reliability with alpha coefficients of .75-.87, except for strength with an internal consistency coefficient of .63⁵⁰. We chose the Hand Function portion of the full SIS for the secondary outcome for several reasons^{51, 52}: 1) it represents a valid and reliable outcome that is well aligned with ICARE specific aims, 2) it can be easily interpreted for clinical meaningfulness, 3) we obtained SIS hand function data from the acute (VECTORS) and post-acute period (Kansas City study) where dynamic change is high and ICARE intervention occurs, and 4) using EXCITE data, there was high correspondence between patient's perception of SIS hand function at two years post, and our laboratory-based primary outcome measure of hand and arm function, the WMFT log mean transformed time score ($r = -0.64$, $p < .0001$, $n = 124$), and other self-report measures including the Motor Activity Log-Amount of use ($r = .68$, $p < .0001$, $n = 124$), and Motor Activity Log-How Well ($r = .68$, $p < .0001$, $n = 124$). This provides evidence for construct validity for this self-report measure. **Clinical**

Meaningfulness: The SIS was developed from focus groups of stroke survivors; the SIS hand function domain lists five activities of the hand that were most important for stroke patients to accomplish; the scale provides a metric of perceived difficulty in performing each of these tasks between 1 (could not do at all) and 5 (not difficult at all). The 5-point scale is normalized to 100% with each integer rating representing a 25-point increment on the normalized scale (e.g., difference between 1 and 2 is 25 points).

Therefore, a 1 category shift in perceived difficulty would represent a 25-point change on the full normalized scale. A minimum of 25 point increase (less difficult) has face validity for a clinically meaningful change and one that can be compared across studies including EXCITE. **EXCITE and SIS:** One year outcome data from the EXCITE trial showed a significant change in self-reported hand function for the CIT compared to the control group. In addition, this improvement on the SIS hand function corresponded with a significant change in WMFT time scores that were significantly greater for the CIT compared to the control group at one year¹⁸. Using a 25 point change (one category), as a measure of successful outcome, we estimated the proportion of subjects in each group who achieved success. At one year, 24% of the control group and 49% of the CIT group (difference of 25%) met this criterion for success. **Acute Time Frame and SIS:** We compared estimates of success rate (i.e., 1 or more category change on SIS hand

function) from three separate sample control groups including, EXCITE (subacute, non equivalent dose), VECTORS (acute, equivalent dose), and Kansas City (1-3 months, non equivalent dose) home-based exercise study³⁵, to more fully anticipate the impact of providing ASAP during a dynamic recovery period. As expected, the estimates of control group success rates from these samples were ordered from acute (46%, n = 13), post-acute (35%, n = 71), to subacute (24%, n = 86).

2.2.3 STUDY # 3: STROKE ARM RECOVERY IN ACUTE/POST-ACUTE STROKE (Winstein PI-HD R03 36212, STAR)

Purpose: The Stroke Arm Recovery trial (STAR) was a single-center, non-blinded, phase II RCT (baseline, post-intervention, 9 mo) that evaluated the immediate and long-term effects of two upper-extremity rehabilitation approaches for stroke arm recovery compared with standard therapy in participants stratified by stroke severity in the acute inpatient rehabilitation setting. The study was conducted at Rancho Los Amigos National Rehabilitation Center, also a site for ICARE. This trial was completed in 2003 with the primary outcomes published in 2004³². **Methods:** Subjects were recruited within 16 days of stroke from inpatient rehabilitation and randomized within severity strata (Orpington Prognostic Scale) into 1 of 3 intervention groups. In addition to standard therapy care (SC) participants were randomized into either functional task-specific practice (FT) or strength-based/impairment training (ST) groups, each of which received 20 additional hours of upper-extremity therapy beyond standard therapy distributed over a 4- to 6-week period across all three groups (i.e., therapy was added to the standard dose of occupational therapy). Because the average inpatient stay became less than 4 weeks (23.1 +/- 11.1d), during the study, the additional time needed to fulfill the 20 hours was completed in an outpatient setting; the same setting we propose for ICARE. Performance measures of impairment (upper extremity Fugl-Meyer motor), strength (isometric torque), and function (Functional Test of the Hemiparetic Upper Extremity), were used. **Results:** Compared with standard care participants, those in the FT and ST groups had significantly greater increases in Fugl-Meyer motor scores ($p = .04$) and isometric torque ($p = .02$) post-treatment. Treatment benefit was primarily in the less severe participants (Orpington Score, ≤ 4.1), where improvement in FT and ST group Fugl-Meyer motor scores more than doubled that of the standard therapy group. Similar results were found for the FTHUE and isometric torque. At the 9 month follow-up, the less severe FT group continued to make gains in isometric muscle torque, significantly exceeding those of the ST group ($p < .05$). At 9 months and despite participant attrition in the less severe cohort, the FT group outperformed the ST group in improvement of upper-extremity isometric torque. In contrast, the performance of the ST group approached the level of the control group while the FT group accelerated its gain in isometric torque over the post-treatment to 9-month interval. This difference at follow-up suggests that therapy contents or its correlates—and not simply therapy dose—was critical to the treatment effect. Surprisingly, the FT group demonstrated better performance than the ST group on a strength measure. One explanation for this counterintuitive result may be that functional task-specific practice provided a more favorable and meaningful context for strength gains that were mediated through persistent daily arm and hand use than the resistance exercises, alone. There is

evidence that intervention strategies that provide context-relevant, meaningful engagement in activities and promote self-management of that activity are more beneficial for skill acquisition and transfer than rote exercises or passive modalities⁵³⁻⁵⁶. *This study and its results factored heavily into the development of the ICARE proposal and more specifically, the task-specific training/impairment mitigation protocol for ASAP.*

2.2.4 STUDY # 4: VERY EARLY CONSTRAINT INDUCED MOVEMENT THERAPY (VECTORS)

Phase II Trial Results (Dromerick PI-NS R21 41261)

Overview: The VECTORS primary result was presented at the International Stroke Meeting in February 2007; manuscript preparation is underway. This trial of CI therapy begins within 14 days of stroke onset, demonstrating the experience of the research team in rehabilitation trials earlier than ICARE or STAR. **Purpose:** VECTORS was a Phase II single center pilot randomized controlled clinical trial of the early application of Constraint Induced Movement Therapy (CIMT). Goals included estimation of effect size, selection of primary endpoints, and determination of safety issues (particularly activity-dependent lesion enlargement. **Methods:** Subjects were assigned using adaptive randomization into the control group (2 hours, traditional OT), a dose-matched CIT group (2 hours shaping, 6h/day constraint), or the high intensity CIT group (3 hours shaping, 90% waking hours constraint) at inpatient rehabilitation admission (**Table 2.2.4**). Inclusion criteria included ischemic or hemorrhagic stroke within 28 days of onset; no prior stroke-related neurologic impairment; need for inpatient rehabilitation; NIH Stroke Scale (NIHSS) aphasia, command, consciousness and sensory items < 1; NIHSS neglect = 0; and persistently hemiparetic UE with some residual voluntary movement. Blinded raters evaluated subjects at randomization, end of treatment (14d), and the primary endpoint (90d). The prespecified primary dependent measure was the total Action Research Arm Test (ARAT) at 90 days after randomization. Mixed model analyses were performed. A subsample (n=9) underwent MRI imaging (apparent diffusion coefficient [ADC] mapping) at study baseline and Day 7-9 to determine if new neuronal injury occurred during study treatment. **Results:** 52 participants (mean age 63.9 + 14 yr) were randomized 9.65 + 4.5 days after onset. Mean NIHSS was 5.3 + 1.8; mean Action Research Arm Test (ARA) score was 22.5 + 15.6; 77% had ischemic stroke. Groups were equivalent at baseline on all randomization variables. As expected, all groups improved with time on the total ARA score. There was a significant time x group interaction ($F = 3.1$ $p < .01$), such that the high intensity CIT group had significantly worse scores at Day 90. No significant differences were found between the dose-matched CIT and control groups at Day 90. Similar time x group interactions were observed using the Wolf Motor Function Test Functional Ability ($F = 3.3$, $p < .01$). No clinical safety issues were encountered; ADC maps revealed no evidence of new neuronal damage. **Conclusion:** Our results did not support the hypothesis that CIT therapy is superior to equal doses of conventional therapy in the acute inpatient rehabilitation setting. A dose response relationship was observed, where a higher dose of CIT was associated with less motor recovery. There was no evidence of activity-dependent lesion enlargement. *Our results highlight the need for clinical trial designs*

that directly and empirically determine the efficacy of specific treatments at specific delivery schedules during each phase of stroke care. ICARE does exactly this.

TABLE 2.2.4 STUDY # 4: VERY EARLY CONSTRAINT INDUCED MOVEMENT THERAPY (VECTORS): PHASE II TRIAL RESULTS (DROMERICK PI-NS R21 41261)

Table 2.2.4	Total Sample	Control	Low CIMT	High CIMT
Age	63.9 ± 14	64.7 ± 14.6	62.8 ± 12.8	64.5 ± 15.5
Days since stroke	9.7 ± 4.6	--	8.8 ± 3.1	9.94 ± 4.8
Total NIHSS	5.3 ± 1.8	5.5 ± 1.8	5.1 ± 1.8	5.31 ± 1.8
Total ARA, impaired	22.5 ± 15.3	19.7 ± 13.9	22.7 ± 14.3	25.4 ± 18.0
FIM Motor	57.8 ± 11.1	56.7 ± 12.2	57.1 ± 9.5	59.8 ± 12.1
% Female	60%	65%	68%	44%
Race				
African American	42%	47%	37%	44%
Caucasian	57%	53%	58%	56%
Stroke Lesion				
% Ischemic	77%	76%	74%	81%

2.2.5 STUDY #5: ICARE PROOF OF PRINCIPLE

Purpose: The purpose of gathering these pilot data was to demonstrate proof of principle for the model of task-specific training that is ASAP: 1) verify our earlier findings that patients who were between 1-3 months could manage the ASAP intervention schedule, comply with the protocol and actively participate; 2) determine recruitment feasibility, enrollment and systematic application of ASAP across multiple sites; 4) successfully implement each of the three elements; 5) demonstrate that therapy applied post inpatient is naturally feasible and safe. There was no control group, evaluators were not blinded, and there was no follow-up; because demonstrating efficacy was not our purpose. **Methods:** Three centers (USC, Emory, NRH) submitted and obtained IRB approval to conduct the study and initially prospectively recruited 6 participants (2/center) within 3 months post CVA; NRH has recently recruited an additional participant whose data are included. Table 2.2.5.a shows data by participant and includes medications and comorbidities. Our sample included diversity in baseline characteristics, initial motor impairment, demographics, and comorbidities. On average per site, 32 participants were referred, 10 were screened, and 2 were enrolled, matching our overall 6% projected capture rate. Each participant received medical clearance and passed a screening evaluation to determine eligibility. The 30 hr dose was the same as our proposal, but we used a more compact distribution of 2 hr/d, 5 d/wk for 3 weeks. In each case, ASAP was administered one-on-one by a trained and standardized intervention therapist who had participated in a 3-day training workshop at USC in spring, 2005. We used the old ASAP protocol, which differed on one dimension from the revised protocol; we did not use a constraint device. Recruitment and training was accomplished but with nine protocol violations, all related to missed treatments that were rescheduled. This along with the other reasons described in Sec 2.1 (Rationale) provided the rationale for a more distributed schedule. We modified the duration to accommodate a more standard outpatient treatment schedule. We found the ASAP protocol to be replicated relatively smoothly across our sites, further supporting our proof of principle.

**TABLE 2.2.5.A STUDY # 5: ICARE MULTI-CENTER PROOF OF PRINCIPLE (ASAP)
PRELIMINARY DATA**

Table 2.2.5.a Proof of Principle Preliminary Data							
	NRH			Emory		USC	
Subject	1	2	3	4	5	6	7
MEDICAL							
CVA Lesion Side (L/R)	R-CVA	R-CVA	R-CVA	L-CVA	L-CVA	L-CVA	R-CVA
Dominant Hand Most Affected	No	No	No	Yes	Yes	Yes	No
Co-morbidities/Past Medical History*	1 - 7	1, 8, 9	10 - 15	1, 12, 16	1	1	1
Medications**	1 - 14	NT	1, 9, 11, 12, 15-17	18, 19	1, 20	21	11, 18, 22, 23
DEMOGRAPHICS							
Race/Ethnicity	AdAm	AdAm	AdAm	AdAm	AdAm	Asian-Am	Caucasian
Age (years)	70	53	71	40	46	62	72
Gender	female	female	male	male	male	male	male
Marital Status (S-single, M-married)	S	S	NA	M	M	S	M
TIMING							
Length of Hospital Stay (days)	11	NA	26	30	28	28	NA
Screen (days since onset)	22	26	85	60	20	26	48
Baseline Eval (days since onset)	22	26	86	79	27	53	49
Post Eval (days since onset)	54	47	109	108	53	84	84
SCREEN							
Ospington Prognostic Scale	NT	NT	NT	0.4	1.2	2	0.8
NIHSS Total	2	6	N/T	2	4	2	2
MMSE	24	29	21	28	28	30	28
Barthel Index (prior to stroke)	95	75	95	100	100	100	100
EVALUATION							
Fugl-Meyer baseline	55	41	54	50	32	38	37
Fugl-Meyer post-intervention	55	41	54	57	53	42	58
WMFT-baseline (avg time in s)	6.20	9.77	6.04	2.56	44.40	28.21	5.75
WMFT-post (avg time in s)	3.57	2.20	2.79	1.60	2.90	63.38	4.59
SIS-Hand (sum)	NT	11	18	NT	NT	NT	NT
SIS Total (sum)	NT	147	242	NT	NT	NT	NT
Brief Self Efficacy (Initial - final)	2-10	5-10	5-10	1-10	7-10	5-7	4-7
Baseline CAHM (average)	20	12.25	58.5	94.5	65.5	30	50
Post-Intervention CAHM (average)	95	NT	NT	100	99.25	57.5	52.6
PHQ 9 baseline	10	18	1	0	4	0	5
PHQ 9 post-intervention	NT	NT	2	NT	NT	0	7
NA = not available; NT = not tested							
* Co-morbidity/Past Medical History codes: 1 HTN, 2 COPD, 3 anemia, 4 sleep apnea, 5 atrial fibrillation, 6 R knee ligament repair, 7 hysterectomy, 8 DM, 9 hypercholesterolemia, 10 pacemaker/bradycardia, 11 seizure disorder, 12 hyperlipidemia, 13 thrombocytopenia, 14 R calf DVT, 15 mild R UE CRPS, 16 hypomagnesemia							
** Medication codes: 1 Coumadin, 2 Cardizem, 3 Prandin, 4 Saxside, 5 Potassium Chloride, 6 Foradil, 7 Flovent, 8 Fluticasone, 9 Pepcid, 10 Lisinopril, 11 Lipitor, 12 Sennas, 13 Lantus, 14 Tylenol, 15 Multivitamin, 16 Plavix, 17 Keppra, 18 Aspirin, 19 Zocor, 20 Norvasc, 21 Benazepril Study, 22 Divan, 23 Niaspin							

TABLE 2.2.5.B INCLUDES A CASE ANALYSIS (PARTICIPANT # 7) THAT MAPS SPECIFIC TASKS AND TRAINING PROCEDURES TO EACH OF THE THREE ASAP ELEMENTS ACROSS THREE DAYS OF TRAINING.

**TABLE 2.2.5.B STUDY # 5: ICARE MULTI-CENTER PROOF OF PRINCIPLE (ASAP)
CASE ANALYSIS-INTEGRATION OF ASAP ELEMENTS**

Case Analysis-Integration of ASAP Elements – Participant #7

Element(s)	Description	Comments
Orientation Session		
MOTIVATION: Collaboration agreement	Participant oriented to ASAP purpose and principles, organization, action planning [optional mitt use]. Future sessions are scheduled.	
MOTIVATION: Task collaboration	S7 designated 4 specific tasks (including ones with bimanual, strength, dexterity requirements), including one as his priority task.	Priority task selected was use of his impaired arm and hand to eat, including management of utensils and mug. Other chosen tasks: card manipulation (shuffling, dealing, holding, placing), writing, handyman tool use (e.g., hammer).
Training Days		
	Assess vitals signs	Within normal limits (all days)
MOTIVATION: Brief Self-Efficacy assessment for priority task	S7 was asked how confident he was to be able to perform specific chosen task. Then asked to problem-solve by providing thoughts on what could be done to increase confidence in next week (S7 Day 1: "Exercise; what else is there?").	Brief self-efficacy assessments 4 times, including first and last sessions. Initial brief self-efficacy score = 4 for eating/management of utensils/mug. Later scores were 5 (middle session) and 7 (end of training).
MOTIVATION and SKILL: Action plans for self-management skills/extended practice	Set-up (end of sessions) and debriefing (beginning of sessions) of participant's action plans.	S7 reported on home tasks of writing and eating with impaired arm/hand (day 8), tasks of writing and lifting boxes in garage (day 15).

Element(s)	Description	Comments
Training Days		
SKILL: task-specific practice (priority task) and IMPAIRMENT MITIGATION: coordination, selective movement, precision; force modulation, and MOTIVATION: collaboration and challenge	Eating skills (use of knife for cutting, pouring liquid into varied size mugs/cups). Progressed from use of knife with built-up handle (Day 1); knife without build-up for cutting around targets in simulated food, drinking from mug filled with varied amounts of water in mug (Day 8); use of knife without built-up handle to cut muffin, break and peel an egg, placed various sized beans into varied size containers. Task practiced for 25-30 minutes in different participant-selected order each day.	S7 limited by decreased grip strength and fine motor control; reported 6 out of 5 difficulty with cutting and 3-4 out of 5 fork and spoon use (Day 1). S7 limited by decreased forearm pronation, shoulder abduction with internal rotation, selective use (coordination) of the arm and hand (Day 8). S7 directed practice session with ideas to increase the level of difficulty and challenge (Day 15).
SKILL: task-specific practice and IMPAIRMENT MITIGATION: speed, intersegmental coordination, selective finger movement, and MOTIVATION: collaboration and challenge	Card manipulation (shuffling, dealing, holding, placing). S7 challenged to speed up movements. Repetitions timed. Task practiced for 25-30 minutes in different order each day.	Day 1: S7 prompted to self-assess difficulty of task and begin problem solving with therapist to increase challenge, implemented 5-point difficulty rating scale. Day 8: S7 dealt cards farther away from midline and body, able to deal and pick-up card faster than previous day. Day 15: S7 chose to vary the type of hand technique to pick up cards, such as finger to thumb, to sliding card to edge of table; reports playing cards with friends.

Element(s)	Description	Comments
Training Days		
SKILL: task-specific practice and IMPAIRMENT MITIGATION: precision; force modulation; coordination; selective movement, and MOTIVATION: collaboration and challenge	Writing (use of pencil for printing and cursive writing). S7 progressed from use of a pencil with built-up handle and pencil manipulation on table top (Day 1), to copying a paragraph, writing in large and small print and cursively (Day 8), to writing without built-up handle, writing on triplicate form, drawing a picture (Day 15). Task practiced for 25-30 minutes in different order each day.	Day 1: S7 required 80.04 seconds to pick up pencil and print name; reported 3 out of 5 difficulty. S7 chose order of writing tasks; stated on day 6 "...writing is a little better...I can read it." S7 reported being pleased with his writing; chose to draw a picture; able to write 3/4 of a page in 10 minutes (Day 15).
SKILL: task-specific practice and IMPAIRMENT MITIGATION: precision; force modulation; load/intensity; endurance work to fatigue; coordination; selective movement, and MOTIVATION: collaboration and challenge	"Handyman" activities (hammering, taking measurements at varied angles, heights, surfaces with ruler and making measurements with pencil; sanding wood; pulling duct tape off a roll and placing on wall at varied heights, plugging cords in/removing from socket). Grip strength targeted. Task practiced for 25-30 minutes in different order each day.	Day 1: missed nail on 10 of 25 attempts; Days 8 and 15: S7 offered suggestions for activity progression based on level of difficulty (e.g., reach farther from body when taking measurements).
MOTIVATION: Task collaboration	Tasks chosen by S7 for next day	Order of tasks practice differed.
	Assess vital signs, pain, and fatigue	Vitals: within normal limits (all days); pain absent; fatigue 6 and 5 out of 10 on Days 8 and 15.
	Exit interview (Day 15)	S7 reported that he resumed playing cards with friends and playing games with grandchildren such as building houses out of cards, coloring, jigsaw puzzles; preparing to get his driver's license and is glad to have practiced writing his signature; reported being pleased with the program and expressed appreciation "... you have changed my life and I thank you."

2.2.6 STUDY # 6: RECRUITMENT FEASIBILITY

Between July and October, 2006, we conducted a feasibility study through systematic chart review of the last 100 stroke admits to each of our clinical sites. The purpose was to determine what percentage of patients would have met inclusion criteria and to determine if our planned recruitment rate was feasible. Because most centers do not routinely administer the NIHSS, Orpington Prognostic Scale, or Fugl-Meyer, we selected alternative measures of upper extremity motor, cognitive, sensory, and neglect that would approximate our criteria, yet be achievable from the chart review. The following criteria were used: 1) presence of distal upper extremity movement (wrist and/or fingers), 2) No severe neglect, 3) UE sensation intact to no more than mildly impaired, and 4) Adequate cognition determined by FIM comprehension and problem solving scores ≥ 4 . **Table 2.2.6** summarizes the results. We estimated of the number of eligible participants/mo by dividing the number eligible by the inclusive months of chart review. From past experience, we estimated that for various reasons, only 75% of those found eligible would be randomized. Our findings suggest there is high probability that each center (Washington DC, Georgia and California) can meet target recruitment goals (3 participants/mo). Additional demographic data (gender, race, age, d/c destination, outpatient occupational therapy referral) and FIM admission and discharge scores were collected.

TABLE 2.2.6 STUDY # 6: RECRUITMENT FEASIBILITY STUDY RESULTS FOR EACH COLLABORATING CENTER

Table 2.2.6 Recruitment feasibility study results for each collaborating center							
Centers	DC	GA	CA				
Sites	NRH	CRM	CFRMC	CSMC	HRMA	LBMC	RLA
Charts Reviewed	100	86	100	100	78	100	100
% Present Wrist/Finger Movement	93.0%	75.6%	68.0%	85.0%	80.8%	77.0%	65.0%
% Severe Neglect	2.0%	14.0%	25.0%	2.0%	12.8%	15.0%	15.0%
% Upper Extremity Sensation Intact or Mildly Impaired	74.0%	79.1%	37.0%	75.0%	85.9%	88.0%	50.0%
% FIM Comprehension ≥ 4	85.0%	72.1%	NA	85.0%	79.5%	76.0%	83.0%
% FIM Problem Solving ≥ 4	79.0%	70.9%	NA	61.0%	70.5%	57.0%	56.0%
% Meet Inclusion Criteria	39.0%	30.2%	32.0%	43.0%	28.2%	38.0%	29.0%
Review Period (mos)	6	9	9	6	20	13	6
Estimated # Eligible (patients/mo)	6.5	3.4	3.6	7.2	1.4	2.9	4.8
Estimated ICARE Recruitment (patients/mo)	4.9	2.2	2.7	5.4	0.8	2.2	3.6
NRH - National Rehabilitation Hospital, Washington, DC;							
CRM - Center for Rehabilitation Medicine, Atlanta, GA;							
CFRMC – Centinela Freeman Regional Medical Center, Los Angeles, CA;							
CSMC - Cedars-Sinai Medical Center, Los Angeles, CA;							
HRMA - Huntington Rehabilitation Medicine Associates, Pasadena, CA;							
LBMC - Long Beach Memorial Medical Center, Long Beach, CA;							
RLA - Rancho Los Amigos National Rehabilitation Center, Downey, CA.							
FIM - Functional Independence Measure (functional item scores range from 1 Total Assistance to 7 Independent; note 4 = Minimum Assistance)							
Estimated ICARE Recruitment - Based upon 75% capture rate							

3 STUDY DESIGN

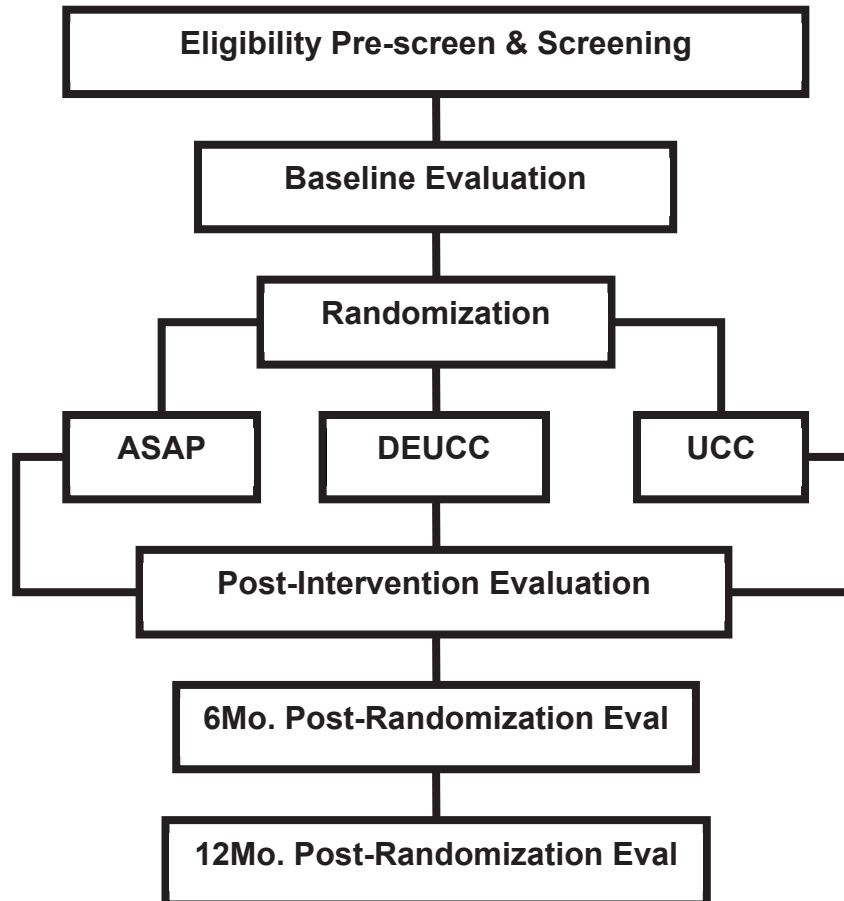
3.1 RESEARCH DESIGN AND METHODS: OVERALL PLAN

The primary objective of the Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE) trial is to conduct a phase III, single-blind, multi-center RCT to compare Accelerated Skill Acquisition Program (ASAP), to a dose-equivalent (DEUCC) control group (Specific Aim 1) and an observational (monitoring only) control group (Specific Aim 2). Our primary outcome is laboratory-based performance of the WMFT measured at 1 year after randomization. ASAP includes 30 hours of one-on-one training delivered over a 10-week duration. We will recruit 360 adults, within 14-106 days of stroke onset, with mild to moderate upper extremity impairment. Participants will be randomized to one of three treatment groups, and the primary dependent measure is change in WMFT time score at 1 year after randomization. Secondary outcome measures will be used to evaluate the impact of treatment interventions on self-perception of paretic hand function and full-scale health status.

This is a multi-site (7 clinical sites), prospective randomized single-blind, clinical intervention trial with recruitment and randomization to occur by the 106th day post-stroke. Participants who are not eligible at the initial screen because they do not exhibit enough recovery may be followed prospectively at the discretion of the site team up to 106 days post stroke. After medical clearance and Baseline Evaluation, participants will be randomized to one of three groups. Please see Figures 3.1 and Section 2.G of the ICARE Manual of Procedures (MOP) for an overview of the study flow.

FIGURE 3.1: OVERVIEW OF THE ICARE DESIGN AND STUDY FLOW

ASAP = Accelerated Skill Acquisition Program; UCC = Usual and Customary Care;
DEUCC = Dose-Equivalent Usual and Customary Care.



3.2 DESCRIPTION OF HOW THE DESIGN FULFILLS THE INTENT OF THE STUDY

Campbell and colleagues define a definitive Phase III randomized clinical trial of a complex intervention as one that, “compares a fully defined intervention with an ‘appropriate alternative’ using a protocol that is theoretically defensible, reproducible, and adequately controlled in a study with appropriate statistical power.”⁵⁷. The ICARE trial is designed to compare ASAP, an integrated set of three essential elements (skill, capacity, motivation) bundled together in a theoretically defensible and reproducible task-specific training protocol, to an equivalent dose of usual and customary outpatient therapy. The dose-equivalent (DEUCC) control comparison is a particularly appropriate alternative given that: 1) the EXCITE design and findings do not rule out the possibility that usual and customary care provided at the same dose and intensity as CIT would have been as efficacious, 2) preliminary findings from VECTORS showed that a higher intensity of CIT applied acutely after stroke was not efficacious, while a lower intensity of CIT yielded comparable results to a dose equivalent usual therapy group, and 3) well designed investigations of upper extremity rehabilitation in the outpatient setting, that compare the effectiveness of task-specific training to that of an equivalent dose of conventional therapy are sorely lacking^{30, 58, 59}. Finally, the non dose-equivalent, observation only group (UCC) will provide important information on the contents of standard outpatient therapy and empirical data on the provision of services that to our knowledge is unknown.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

Eligibility & Study Enrollment are described in detail in section 2.H of the ICARE Manual of Procedure. Consent is described in detail in Section 2.I of the ICARE Manual of Procedure

4.1 INCLUSION CRITERIA

4.1.1 DISEASE OR DISORDER UNDER STUDY, AND HOW IT IS TO BE DOCUMENTED

Diagnosis of stroke: Participants will be individuals with a recent onset cerebral vascular accident, stroke event. A stroke is defined according to the World Health Organization (WHO) definition as, “a rapid onset event of vascular origin reflecting a focal disturbance of cerebral function, excluding isolated impairments of higher function and persisting longer than 24 hours.” Clinical assessment and a CT or MRI scan will confirm the diagnosis.

4.1.2 CLINICAL INDICATORS OF CURRENT STATUS, AS MEASURED PRIOR TO RANDOMIZATION

Inclusion and Exclusion criteria will be determined through chart review, participant interview and the physical screening instruments performed by the Clinical Site Coordinator, Physician Investigator and qualified recruiting personnel. The Baseline Evaluation will be used to confirm eligibility that might have changed during this dynamic period of recovery. The Physician Investigator will perform a brief medical examination just prior to baseline and provide documented clearance for participation in the study. If greater than 72 hours pass from the time of the Brief Medical Exam to the

Baseline Evaluation, a Licensed Therapist Recruiter or the Site Physician will reassess the participant to rule out an interceding stroke event prior to initiating the Baseline Evaluation. Participants who are not eligible at the initial screen because they do not demonstrate enough recovery, may be followed prospectively at the discretion of the site team up to 106 days post stroke. Stroke diagnosis will be confirmed via CT or MRI. If there is no confirmatory neuroimaging but all other inclusion/exclusion criteria are met, Dr. Dromerick, Principal Investigator and a board-certified neurologist, will review the available pre-screen, screen and medical records to confirm the clinical diagnosis of stroke based on the ICD-9 criteria and we will document the non-imaged status for tracking purposes.

Clinical Indicators for eligibility include: (see ICARE MOP Section 2.H for complete Eligibility Criteria)

Inclusion Criteria

1. Diagnosis of ischemic or intraparenchymal hemorrhagic stroke, within the last 106 days
2. Presence of paresis in an upper extremity
3. Age 21+
4. Able to read & verbalize effectively in English or Spanish
5. Willing to attend outpatient therapy & f/u evaluations to 1 year
6. Signed consent

4.1.3 PRIOR THERAPY

Participants will be randomized on or before the 106th day post-stroke. They will have likely received one or a combination of physical therapy, occupational therapy and speech therapy as an inpatient or home health patient. For this study it is anticipated that prior inpatient and home health therapies will be balanced amongst the treatment groups. They will be documented and, if imbalance is identified, treated as covariates. Outpatient occupational therapy treatment hours will be measured during screening and again at the Baseline Evaluation as a final check for eligibility. Participants may have had up to, but no more than, 6 hours of outpatient occupational therapy treatment prior to randomization to be eligible for this study. Neither outpatient occupational therapy **evaluation** nor home health will be counted toward the 6 hour maximum allowed.

4.1.4 DEMOGRAPHIC CHARACTERISTICS AS APPLICABLE

Our Inclusion/Exclusion criteria are designed to capture the increasing number of surviving stroke patients who have a significant motor impairment, but whose deficit is not significant enough to prevent participation in an intense, focused therapy program. No inclusion/exclusion criteria will be based on gender, childbearing potential, and race or ethnic origin. Children and adolescents under the age of 21 will be excluded on scientific grounds. The incidence, etiology and pathophysiology of stroke are quite different in this age range, and inclusion would introduce substantial heterogeneity to the subject pool without providing a large enough sample to inform pediatric stroke care.

More importantly, patterns of recovery differ with age, and adding small numbers of subjects with very different recovery from the target population would similarly impede hypothesis testing.

4.2 EXCLUSION CRITERIA

Participants will be pre-screened and screened for eligibility prior to randomization on or before the 106th day post stroke.

Clinical Indicators for eligibility include: (see ICARE MOP Section 2.H for complete Eligibility Criteria)

Exclusion

1. Inability to communicate in English or Spanish
2. Dx of stroke with severe intraventricular extension or subarachnoid hemorrhage
3. History of psychiatric illness requiring hospitalization during the past 24 months
4. Active drug treatment for dementia
5. Neurologic condition that may affect motor response (e.g. Parkinson's, ALS, MS)
6. UE musculoskeletal injury limiting use prior to stroke
7. History of head trauma requiring hospitalization within last 12 months.
8. Positive toxicology screen for illegal substances or treatment for alcohol withdrawal since index stroke
9. UE amputation of all fingers or thumb of hemiparetic limb
10. Treated with Botox in affected arm within last 3 months.
11. No active finger extension
12. UEFM motor score <19 or >58

4.2.1 SPECIFY ANY EXCLUSION RELATED TO PREGNANCY,
Exclusions Related to Pregnancy, Lactation Or Plans To Become Pregnant
Not applicable.

4.2.2 USE OF EXCLUDED DRUGS, DEVICES, ETC. WITHIN 2 DAYS PRIOR TO
STUDY ENTRY

1. Treated with Botox in affected arm within last 3 months.
2. Active drug treatment for dementia
3. Treatment for alcohol withdrawal since index stroke

4.2.3 SPECIFY ANY CLINICAL OR OTHER CHARACTERISTIC THAT PRECLUDES
APPROPRIATE DIAGNOSIS

Specify Any Clinical Or Other Characteristic (Life Expectancy, Co-Existing Disease),
Demographic (Age) Or Other Characteristic That Precludes Appropriate Diagnosis,
Treatment Or Follow-Up In The Trial (See MOP Section 2.H for complete eligibility
criteria)

1. Inability to communicate in English or Spanish
2. Dx of stroke with severe intraventricular extension or subarachnoid hemorrhage

3. History of psychiatric illness requiring hospitalization during the past 24 months
4. Active drug treatment for dementia
5. Neurologic condition that may affect motor response (e.g. Parkinson's, ALS, MS)
6. UE musculoskeletal injury limiting use prior to stroke
7. History of head trauma requiring hospitalization within last 12 months.
8. Positive toxicology screen for illegal substances or treatment for alcohol withdrawal since index stroke
9. UE amputation of all fingers or thumb of hemiparetic limb
10. Treated with Botox in affected arm within last 3 months.

4.2.4 ACTIVE DRUG OR ALCOHOL USE OR DEPENDENCE

Active Drug Or Alcohol Use Or Dependence That, In The Opinion Of The Site Investigator, Would Interfere With Adherence To Study Requirements

1. Positive toxicology screen for illegal substances or treatment for alcohol withdrawal since index stroke
2. Affirmative response to at least 2/4 CAGE alcohol questionnaire without eligibility waiver by Center PI.

4.2.5 SERIOUS ILLNESS

Serious Illness Until Participant Either Completes Therapy Or Is Clinically Stable On Therapy, In The Opinion Of The Site Investigator, For At Least 14 Days Prior To Study Entry (See MOP Section 2.H for complete eligibility criteria)

1. Dx of stroke with severe intraventricular extension or subarachnoid hemorrhage
2. History of psychiatric illness requiring hospitalization during the past 24 months
3. Active drug treatment for dementia
4. Neurologic condition that may affect motor response (e.g. Parkinson's, ALS, MS)
5. UE musculoskeletal injury limiting use prior to stroke
6. History of head trauma requiring hospitalization within last 12 months.
7. Positive toxicology screen for illegal substances or treatment for alcohol withdrawal since index stroke
8. UE amputation of all fingers or thumb of hemiparetic limb
9. Not expected to be available for all study activities \leq 1 year due to illness (cardiac disease, malignancy, etc.) CSC & Site Physician must concur

4.2.6 INABILITY OR UNWILLINGNESS TO GIVE WRITTEN INFORMED CONSENT

Inability Or Unwillingness To Give Written Informed Consent Of Participant Or Legal Guardian/Rep To Give Written Informed Consent

1. Inability to give informed consent for study participation

2. Expressed disinclination/reluctance and/or inability by participant to attend outpatient therapy 2-3x a wk for up to 10 weeks, and attend all follow-up evaluations.
3. Family/caregiver expressed disinclination/reluctance and/or inability to support participant to attend outpatient therapy 2-3x a wk for up to 10 weeks, and attend all follow-up evaluations.

4.3 STUDY ENROLLMENT PROCEDURES

Study Enrollment is described in detail in Section 2.H of the ICARE Manual of Procedure. Consent is described in detail in Section 2.I of the ICARE Manual of Procedure.

4.3.1 IDENTIFICATION AND RECRUITMENT OF PARTICIPANTS

Participants will be 360 women and men 21 years of age or older, recruited from among individuals with a diagnosis of stroke who are admitted to one of the study inpatient facilities or an affiliate facility or who have been discharged directly home from an acute facility, but with mild to moderate upper extremity impairments or who are directly referred to study personnel. Children, defined by NIH criteria as < 21 years have been excluded on scientific grounds. The incidence, etiology and pathophysiology of stroke are quite different in this age range, and inclusion would introduce substantial heterogeneity to the subject pool without providing a large enough sample to inform pediatric stroke care. More importantly, patterns of recovery differ with age, and adding small numbers of subjects with very different recovery from the target population would similarly impede hypothesis testing. The expected demographics summarized in Table 4.3.1 by site and based on 2006 Rehabilitation Stroke Admissions represent those of the geographical areas participating in ICARE. Our Inclusion/ Exclusion criteria are designed to capture the increasing number of surviving stroke patients⁶³ who have a significant motor impairment, but whose deficit is not significant enough to prevent participation in an intense, focused upper extremity therapy program. Our criteria are relevant to the dimensions of motor impairment and participation including: medical stability, physiological stability, cognitive and motor capability and do not exclude a sizable proportion of stroke survivors who may have other common sequelae of stroke including depression. We carefully chose instruments that have a high level of specificity for ICARE criteria. Based on previous work, the demographic and prognostic literature for UE recovery^{64, 31, 61, 65}, and the earlier timing (compared to EXCITE) for this intervention trial, we expect to capture the majority of eligible participants who otherwise might be overlooked in the current environment. Updated with 2005 statistics, Table 4.3.1 shows that between 62% and 80% of stroke admissions to our inpatient sites are discharged back to the community (home) and could be eligible for outpatient services.

The clinical site coordinator, site physician or other qualified site personnel will perform an Express Chart Screen (ECS) on all stroke patients admitted to participating facilities and all referrals to the ICARE trial within 106 days post stroke. If the participant passes the Express Chart Screen, a HIPAA Authorization and Screening informed consent will

be obtained. Following HIPAA Authorization and Screening Consent, a Brief Clinical Screen will be performed that includes 3 items of the NIHSS, motor component of the upper extremity Fugl-Meyer, Barthel for pre-morbid status and PHQ-2 screen for depression. Presently, the average inpatient stay for an uncomplicated stroke is less than 1 week for acute management. The patient is usually discharged to inpatient rehabilitation an extended care facility or home, often with referral to home health or outpatient therapy. It is during these transitions between levels of care that it is normally determined if the patient is a candidate for more rehabilitation, and the option of out-patient rehabilitation is discussed with the patient and family/caregiver. Our study flow allows for a detailed Clinical Screen close to that time and provides an opportunity to re-screen prospective participants who may have needed additional recovery time to qualify for the study. The timing and setting for the ICARE study is therefore consistent with usual and customary care decision making about future rehabilitation needs and the knowledge that this is a dynamic period of change. The Study Informed Consent will be presented close to the time that decisions about out-patient therapy are normally considered. If the patient does not want to make a decision about participation at that time, s/he will be given the opportunity to take the consent home and contact study staff at a later time should s/he wish to participate, but as long as it is prior to his/her 106-day anniversary from stroke onset and s/he has not received more than 6 hours of outpatient occupational therapy.

Enrollment will commence when the participant signs the Study Informed Consent. We expect this to be near the time of discharge from inpatient care or the beginning of outpatient occupational therapy. Candidates who pass the Brief Clinical Screen will be followed by the Clinical Site Coordinator, and administered the Detailed Clinical Screen near the expected evaluation for outpatient occupational therapy referral. Candidates who pass the Detailed Clinical Screen will be provided a Study Informed Consent and Videotaping Informed Consent. Those who do not pass initially may be held for rescreening at the discretion of the Clinical Site Coordinator and the Site Physician, provided that it is prior to his/her 106-day anniversary from stroke onset and has not received more than 6 hours of outpatient occupational therapy.

A Brief Medical Exam (BME) will be conducted by the study Site Physician just prior to the Baseline Evaluation. At the BME, the physician will physically examine the participant; administer, or at a minimum review, the NIHSS & PHQ-9 scores, and rule out an interceding stroke event to confirm eligibility. The BME is documented via ICARE Form MR3. Participants who pass the Brief Medical Exam, will proceed to Baseline Evaluation. If, at the Baseline Evaluation, greater than 72 hours have passed since the Brief Medical Exam, a Licensed Therapist Recruiter or the Site Physician will reassess the participant to rule out an interceding stroke event prior to initiating the Baseline Evaluation. Once an interceding stroke event has been successfully ruled out, the Blinded Evaluator will administer the UE Fugl-Meyer, motor component, and provide the raw data to the Clinical Site Coordinator who will make a final determination of eligibility. Those with a score less than 19 or greater than 58 at the Baseline Evaluation are not eligible participants for the ICARE study. After full compliance with all inclusion

and exclusion screening criteria, and medical release from the Site Physician Investigator, the baseline evaluation will proceed. Randomization will be done after the Baseline Evaluation is completed and eligibility is confirmed. Therefore, prior to randomization, participants will have completed the baseline evaluation and all relevant stratification variables (days from stroke onset and UEFM score) entered into the ICARE database via the secure web data-entry system.

TABLE 4.3.1 STROKE ADMISSIONS, DEMOGRAPHICS AND DISCHARGE CHARACTERISTICS FOR EACH COLLABORATING CENTER

Table 4.3.1 Stroke admissions, demographics, and discharge (DC) characteristics for each collaborating center							
Centers	DC	GA	CA				
Sites	NRH	CRM	CFRMC	CSMC	HRMA	LBMHC	RLANRC
2006 Rehab stroke admissions	466	249	248	210	94	171	422
% Female	51.07%	50.00%	54.84%	54.30%	44.68%	51.46%	37.20%
% White	25.97%	33.00%	20.67%	81.01%	72.34%	52.63%	11.99%
% African-American	67.17%	53.00%	53.51%	12.90%	7.45%	16.37%	20.14%
% Hispanic	2.15%	4.00%	0.00%	1.00%	3.19%	11.11%	52.76%
% Native Hawaiian or Other Pacific Islander	0.00%	0.00%	5.18%	0.00%	0.00%	1.23%	0.01%
% American-Indian	0.00%	0.00%	0.00%	0.01%	1.06%	0.00%	0.00%
% Asian	1.72%	1.00%	0.00%	5.21%	15.96%	11.70%	13.43%
% Other	3.00%	9.00%	20.64%	0.00%	0.00%	7.02%	0.00%
Mean age (yrs)	63.97	56	70.59	74	70	68.42	57.25
Age range (yrs)	15-97	18-88	—	31-105	30-95	26-96	18-89
% DC to home	72.53%	80.00%	74.60%	76.70%	63.83%	74.70%	76.30%
Mean Admission FIM per selected subgroup:							
Self Care	16.49	19.1	18.85	18.68	23.93	19	13.78
Mobility	5.96	7	11.56	12.05	7.24	7.4	8.7
Motor Subtotal	31.25	35.1	37.73	33.66	32.2	34	25.62
Cognitive Subtotal	24.88	20.6	18.11	21.51	22.5	17.9	18.35
Total FIM	55.95	55.6	55.84	57.28	56.71	53.7	45.17
Mean DC FIM per selected subgroup:							
Self Care	29.01	27.3	27.26	26.51	36.22	27.6	27.38
Mobility	13.27	12.4	18.55	23.28	13.71	12.6	20.24
Motor Subtotal	61.58	55.1	54.82	49.35	52.76	51.5	50.52
Cognitive Subtotal	27.92	24.6	20.79	23.39	25.14	21.5	22.17
Total FIM	89.63	79.7	75.61	76.57	82.30	77	76.65
Average rehab LOS	22.71	18	15.21	12	15.65	15.6	24.15
NRH - National Rehabilitation Hospital, Washington, DC							
CRM - Center Rehabilitation Medicine, Atlanta, GA							
CFRMC - Centinela Freeman Regional Medical Center, Inglewood, CA							
CSMC - Cedars-Sinai Medical Center, Los Angeles, CA							
HRMA - Huntington Rehabilitation Medicine Associates, Pasadena, CA							
LBMHC - Long Beach Memorial Medical Center, Long Beach, CA							
RLANRC - Rancho Los Amigos National Rehabilitation Center, Downey, CA							
FIM - Functional Independence Measure (functional item scores range from 1 Total Assistance to 7 Independent; note 4 = Minimum Assistance)							

4.3.2 PROCEDURES FOR DOCUMENTATION OF REASONS FOR INELIGIBILITY And For Non-Participation Of Eligible Participants

If participants are excluded, reasons for exclusion will be recorded via ICARE Summary Forms PSF1, SF11 & EF16, but no patient identifying information will be reported.

4.3.3 CONSENT PROCEDURES

HIPAA Waivers have been granted by all participating clinical sites' Internal Review Boards for the Pre-Screen to determine eligibility (Express Chart Screen). A HIPAA Authorization and Screening Informed Consent will be attained prior to the Brief Clinical Screen and later Detailed Clinical Screen. Candidates who meet the screening eligibility criteria, will be given the Study Informed Consent by the Clinical Site Coordinator or qualified recruitment personnel and asked to sign both the Study Informed Consent and a consent to be videotaped. Simultaneously, we will notify the primary care physician of his/her patient's participation in ICARE, via ICARE Form MR1. Please see MOP Section 2.I for samples of the Informed Consents and HIPAA Authorization.

4.3.4 DESCRIPTION OF PROCEDURE FOR OBTAINING INTERVENTION GROUP ASSIGNMENTS

After full compliance with inclusion and exclusion criteria, medical clearance from the site Physician Investigator, and completion of baseline evaluations, a total of 360 participants will be randomized. Participants randomized to either ASAP or DEUCC will undergo 30 hours of outpatient therapy distributed over a 10-week (max of 16 weeks post-randomization) duration that best accommodates the participant's and clinician's schedule. Participants randomized into UCC will be monitored only during the 16-week post-randomization intervention period. Outpatient occupational therapy records will be collected for this period, from which the Clinical Site Coordinator will complete the ICARE intervention documentation. Treatment allocation will occur after baseline assessment no earlier than 14 days and no later than 106 days post-stroke.

5 STUDY INTERVENTIONS

Study Interventions are described in detail in Section 2.K of the ICARE Manual of Procedure.

5.1 INTERVENTIONS, ADMINISTRATION, AND DURATION

Participants will be randomly assigned to one of three interventions: ASAP, UCC or DEUCC. ASAP will take place at the clinical site's outpatient clinic or affiliated outpatient clinic by a standardized ASAP licensed occupational or physical therapist. UCC is a monitoring group only. It will be executed at the site and by the personnel that would be usual and customary for the participant exclusive of the study. DEUCC consists of 2 phases: the first mimics UCC and will be executed at the site and by the personnel that would be usual and customary for the participant exclusive of the study; the second phase will take place at the clinical site's outpatient clinic or affiliated outpatient clinic by a licensed occupational therapist. For each of the (3) treatment groups, all intervention will occur between randomization and 16 weeks post-randomization. Access to the outpatient occupational therapy records of the participant is required; these will be obtained by the recruiting site. HIPAA Authorization will be provided by the participant for this purpose. The requested site-specific outpatient occupational therapy records shall include, but are not limited to: Initial Evaluation, Daily Treatment Records, Progress Notes/Records, SOAP Notes, Exercise Logs, Home

Exercise Programs, Records for Billing Department and Billing Records, Therapy Prescriptions, Equipment & Orthotic Prescriptions and Discharge Planning & Evaluation documents. These records will be scanned and uploaded to a secure ICARE web-site as directed by the Data Manager in Section 2.T.5 of the ICARE MOP.

Vital signs, as well as any symptoms of fatigue, stress or dehydration will be monitored during each session in accordance with usual and customary standard practice. For further details about each treatment group, please see MOP Section 2.K

5.1.1 ACCELERATED SKILL ACQUISITION PROGRAM (ASAP) INTERVENTION

The Accelerated Skill Acquisition Program (ASAP) training intervention is a fully defined protocol that is based on the fundamental elements of **skill** acquisition through task-specific practice, impairment mitigation to increase **capacity**, and **motivational** enhancements to build self-confidence. It is grounded in the following evidence-based principles: Effective rehabilitation of the paretic upper extremity is achievable and based upon the provision of challenging, intensive, and meaningful task practice for motor skill acquisition, mitigation of associated linchpin impairments and dysfunctions of movement, and the confidence to integrate use of emerging skills into daily life^{5, 15, 16, 64, 67}. Eight principles are used to guide ASAP intervention sessions: 1) Ensure challenging and meaningful practice^{16, 28, 29, 68, 69}, 2) address important mutable impairments⁷⁰⁻⁷³, 3) enhance motor capacity through overload and specificity^{74, 75}, 4) preserve natural goal-directedness in movement organization^{76, 77}, 5) avoid artificial task breakdown when engaging in task-specific practice⁷⁸, 6) active patient involvement and opportunities for self-direction are feasible and desirable^{54, 79}, 7) balance immediate and future needs for efficient motor skill and capacity enhancement with the development of confidence and self-management skills^{80, 81}, and 8) drive task-specific self-confidence (self-efficacy) high through performance accomplishments⁸².

ASAP protocol parameters: The program begins with an orientation session to: 1) prepare the collaborative real-world task list to be used during training; it includes 6 tasks the patient most wants to perform with at least two, a bimanual activity, two a strength-dependent activity including the most-affected arm, and two activities requiring dexterity of the most affected hand, 2) designate a priority or benchmark task from the collaborative task list, 3) determine fundamental impairments and the challenge point(s) or breakdown point(s) for a minimum of the priority/benchmark task, 4) prepare a collaborative schedule for the first day of training, 5) introduce the participant to the mitt and its function, 6) orient the participant to the brief self-efficacy question, 7) orient the participant to out-of-lab action plans (i.e., homework), 8) orient the participant and trainer to roles during the 10-weeks of training, and 9) obtain participant signature on the partnership agreement. Training sessions are 3x per week for a total of 30 hours, with rest breaks as needed, but kept to a minimum. Each training session begins with collaborative ordering of the real-world tasks identified at the orientation session. The real-world tasks may change as interests and goals evolve, however the priority task may not change. Task and movement analysis is done for each real-world task to determine the key movement dysfunctions or impairments. The goal of intervention

training is to focus attention and effort directly on the problematic area (i.e. dysfunction, impairment) to facilitate skill acquisition without simply providing a compensatory strategy as a quick fix to the problem. Classic physiologic-like overload parameters are used to drive progress. Practice activities within real-world tasks are selected based on patient perspective/preference. Training is collaborative and interactive with the participant actively participating in problem-solving and assessing performance. Confidence building and empowerment is embedded in the training and education. Self-efficacy assessment is done 4 times throughout the training period using the Brief Self-Efficacy Rating Scale and a follow-up question aimed at self-directed progression. Participants will be asked to sign a partnership agreement contract. Included in their responsibilities is to perform inter-session 'action plans' or out of lab activities. The assignments encourage specific practice in the home or community setting. Examples include finding a challenging task involving food preparation or eating or reading an education handout about motor recovery. Participants are asked to report on the effectiveness of their action plan assignment on the next day of training before the practice session begins that day. A comprehensive Manual of Operations for ASAP is available on the secure website. Access is granted to all ASAP therapists and their back-ups after signature is obtained on a Confidentiality and Nondisclosure Use Agreement and a brief orientation meeting.

ASAP Schedule: ASAP includes (1) 2-hour orientation and evaluation session followed by 30 hours of one-on-one training delivered in 1-hour segments, 3x/week over 10 weeks. Therapy may extend up to 16 weeks post-randomization to make up for missed sessions due to illness or other unavoidable absences, but will exceed neither 16 weeks post-randomization nor 30 hours in total.

5.1.2 USUAL AND CUSTOMARY CARE THERAPY (UCC)

UCC is a monitoring group only. It will be executed at the site and by the personnel that would be usual and customary for the participant exclusive of the study. While several studies describe and evaluate usual occupational therapy during inpatient rehabilitation⁸³⁻⁸⁶, we identified no published study that documents such therapy specifically in the post-acute outpatient context. Further, Medicare records indicate that the quantity of outpatient care is rapidly changing, partially in response to the Balanced Budget Act of 1997 and its sequelae⁸⁷. We conducted an informal survey of 25 licensed Occupational Therapists working in outpatient, hospital-based settings across the country to determine standard therapeutic practices for individuals post-stroke, with emphasis on recovery of upper extremity function. Sixty percent of the survey respondents had greater than 10 years of clinical experience, and almost three-quarters had been practicing for at least 5 years. Therapists were asked to write-in the typical interventions employed, based on their experiences and practices of their colleagues. Analysis of responses revealed 5 major categories of post-stroke UE intervention: 1) Functional Task and I/ADL training (21 respondents=84%), 2) Posture and neuromuscular rehabilitation (20 respondents= 80%), 3) Weight-bearing and strengthening activities (19 respondents=76%), 4) Range of Motion exercises (12 respondents= 48%), and 5) Modalities (stimulation, ice, heat, etc.) (19

respondents=76%). These results are consistent with the American Occupational Therapy Association (AOTA) published practice guidelines for adults with stroke. AOTA guidelines specify that "the goal of therapy is to increase "function" and "intervention addresses both the component deficits [such as postural and motor control, muscle strength and tone] and the context of the client's life". Furthermore, the guidelines list treatment techniques for adults with stroke, including: Functional mobility training, Compensatory techniques for ADL, Neuromuscular facilitation and inhibition techniques, Motor control retraining, Weight-bearing techniques, Strength and endurance techniques, Self range of motion techniques, and Physical agent modalities. We expect the UCC intervention for ICARE to be representative of a typical UE intervention for adults with stroke, as supported by both these national practice guidelines and our survey results of clinical practice.

UCC Protocol Parameters: *(Note: These parameters are provided to aid the ICARE team in documenting the UCC intervention. As a monitoring only group, the ICARE trial and trialists should not influence provision of care or content of therapy.)* Prior to intervention sessions (visits), the participant will attend a standard outpatient Occupational Therapy evaluation session in accordance with usual and customary practice during which an initial therapy prescription (treatment plan and dosing schedule) will be determined. The evaluation during which the initial therapy prescription is determined may pre-date randomization; a separate evaluation for ICARE purposes should not be completed. The UCC group will receive Occupational Therapy for the upper extremity as determined by each participant's individual therapist, based upon usual and customary practice standards. The therapists are free to design and implement treatment according to their usual practice. We require access to all treatment documentation and relevant billing records for study participants randomized to UCC. This is an observation only group with no a priori stipulation of the number of visits. Documentation is similar for UCC and DEUCC.

UCC Schedule: The number of visits and frequency for the intervention is determined per the therapy prescription and the usual and customary financial resources and practices thereof (i.e. private insurance, HMO, Medi-cal, Medicare, etc.). Only outpatient occupational therapy treatment that occurs between randomization and 16 weeks post-randomization will be recorded as intervention for this group.

5.1.3 DOSE-EQUIVALENT USUAL AND CUSTOMARY CARE THERAPY (DEUCC)
DEUCC consists of 2 phases. The therapists are free to design and implement treatment according to their usual practice. The number of visits is constrained to 30 to comply with the ASAP therapy dose. The first phase mimics UCC and will be executed at the site and by the personnel that would be usual and customary for the participant exclusive of the study; the second phase will take place at the clinical site's outpatient clinic or affiliated outpatient clinic by a licensed occupational therapist. The site coordinator will inform the treating therapist of this stipulation only after the prescriptive dose has been determined and documented. The site coordinator or designated

research assistant will monitor the actual number of visits, document it and the contents of the therapy sessions as described in the MOP Section 2.K.

DEUCC Protocol Parameters: Participants in the DEUCC group will initially receive outpatient Occupational Therapy for the upper extremity metered according to the therapy prescription in a manner identical to the UCC group. This is the usual and customary care (UCC) phase of the DEUCC intervention. As the participant is nearing the end of the recommended dose of UCC, the Clinical Site Coordinator will inform the Participant and Therapist that the Participant has been randomized to DEUCC and thus is eligible to continue with therapy until a total balance of 30 hours of therapy has been reached. The onset of the DEUCC phase will then begin to reach the requisite 30 hours of outpatient occupational therapy within the 16 weeks post-randomization intervention window. Therapy content will continue to be guided by usual and customary practice. The Clinical Site Coordinator and Site Physician will determine the appropriate time for knowledge of DEUCC treatment group assignment to be shared on an individual basis. Both the therapist and the Participant will have knowledge at the time of consenting that this may be a possible scenario, and will also have the knowledge that treatment group assignment into DEUCC will not be disclosed until near the end of the UCC portion of treatment. Ideally, the 30 hours of therapy will be distributed into 1 hour treatment sessions, 3 times per week for 10 weeks in order to match the ASAP dose schedule. Therapy may extend up to 16 weeks post-randomization to make up for missed sessions due to illness or other unavoidable absence, shorter treatment sessions or fewer sessions per week as may be usual and customary at some facilities, but the total dose will exceed neither 30 hours nor 16 weeks post-randomization.

DEUCC Schedule: DEUCC includes 30 visits of one-on-one or group therapy ideally delivered over 10 weeks. Therapy may extend up to 16 weeks post-randomization to make up for missed sessions due to illness or other unavoidable absences, but will exceed neither 16 weeks post-randomization nor 30 hours in total.

5.2 HANDLING OF STUDY INTERVENTIONS

5.2.1 STANDARDIZATION PROCEDURES FOR THE INVESTIGATIONAL INTERVENTION GROUP

Evaluation of training procedures is important for: 1) assuring standardization across study sites; 2) providing feedback from the training center to all site personnel concerning administration of techniques; and 3) providing possible explanations for ICARE results in the event of non-standard administration. The standardization process including initial training and maintenance throughout the trial is detailed in the Accelerated Skill Acquisition Program Manual of Procedures (ASAP MOP) and Section 2.U.2 of the ICARE Manual of Procedures. It is designed to provide constructive feedback to personnel and ultimately improve their performance with protocol administration. Briefly, the initial training includes a two-phase process with Phase 1 competency tested at the conclusion of a 5-day investigator training workshop held during the start-up phase. For newly added ASAP therapists, the regional center or

local site is responsible for providing this training via its already trained, standardized therapists. Phase II competency will be completed through self-study of the interactive ASAP MOP, accessed on designated study-supplied computers and with streaming, pilot-and volunteer-subject digital video examples interspersed throughout. Phase II competency will be assessed via successful completion and submission of three ASAP procedures through videorecorded demonstrations and accompanying documentation and completion of one knowledge test.

An ASAP MOP was developed at the Administrative Coordinating Center; reviewed and edited by the Executive Committee and has been disseminated by the Data Management Center to each clinical intervention site, across the secure web-site to the local study-supplied computers at each clinical intervention site. It includes all details for the intervention protocols, standardization training procedures, instructions on measures, and all data collection forms (clinical report forms). Use of the MOP, standardization and re-standardization of study personnel as well as regular monitoring site visits will ensure systematic delivery of the investigational intervention across sites. A dynamic version of the ASAP MOP will be available on the secure ICARE website. The ASAP therapists and back-ups will be notified by blast emails whenever there is a change in the ASAP MOP, study report forms or resource documents.

Training of all intervention therapists will occur during the first year of the study, in the start-up phase (**Table 5.2.1**). Our first Investigator training workshop was held July 19-23, 2008 at USC. Relevant training material including powerpoint presentations, video demonstrations and supporting documents from that training meeting are available to designated study personnel on the secure ICARE website.

The initial training activity was led by the ASAP Intervention Team (Blanton, Nelsen, Lewthwaite and Winstein). ASAP intervention therapists attended a 5-day training workshop in Los Angeles to accomplish Phase I competency in administration and documentation of a complete dose (30 hrs). For Phase II competency, each interventionist was videoed off-site during administration of each element (task-specific training; impairment mitigation; motivational enhancements) with study volunteers (pilot participants). Follow-up videotapes of the intervention therapist during the 1st and 20th treatment session with his/her first ASAP participant were required for Phase III certification. This is repeated for recertification at least every six months for the remainder of the project.

TABLE 5.2.1 ICARE GANTT CHART

Table 5.2.1 ICARE Gantt Chart																				
Trial Timeline																				
	Year 1				Year 2				Year 3				Year 4				Year 5			
Quarters	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Manual of procedures finalized																				
Standardization training and certification (all three groups)																				
Web based data entry and tracking finalized																				
HIPAA and IRB approval (all sites)																				
Monitor Usual Occupational Therapy																				
Staff recruitment																				
Supplies/Equipment procured																				
Field training (data entry etc.)																				
Recruitment material																				
Participant recruitment																				
Intervention and follow-up																				
Data analysis (interim analysis)																				
Publication preparation																				
The gray areas indicate the period in which the activities are performed.																				

Evaluation of all training videotapes will be conducted by the appropriate experts from the ASAP Intervention Team. We will use the consensus model approach where a rater pair observes a set of videotapes. They subsequently discuss each performance observed and, by consensus, provide one rating for each category on the administration rating sheet. As a general rule, each panel (2 individuals) observes a videotaped segment of the tape, discusses the performance, and decides upon the most appropriate rating for the videotaped segment. Individuals selected for the panels will be either longstanding members of the EXCITE research project here at USC or with experience conducting examinations and applying rehabilitation interventions in other studies to persons with neuromuscular dysfunction. New rating panel members will be trained by the Training Center Director (Monica Nelsen, DPT) or Co-Director, (Sarah Blanton, DPT). Once rated, the completed recording sheets and summary of results will be returned to the individual rated via email with a record kept at the training center. Additionally, the results will be shared with the site Physician Investigator. All results will be monitored and further analyzed by the ICARE Training Center staff. To gain approval for administration of ASAP, the performance of a site must be equal to or greater than 90% criterion. Standardization will continue throughout the duration of the study. The Clinical Research coordinator and Principal Investigators are responsible for maintaining standardization and competency throughout the trial. All new staff or back-up intervention therapists will be required to procure full certification before being eligible to administer the investigational treatment.

Standardization will continue throughout the duration of the study. Specific filming procedures are described in the MOP Section 2.U.2. The Clinical Site Coordinator and Principal Investigators will be responsible for maintaining standardization and competency throughout the trial.

Communication between the ASAP Therapists, Study PI, Sub-Investigator (Lewthwaite) and Project Coordinator will be maintained through conference calls to review and discuss any training questions, adverse events, or other concerns. A secure web-based Discussion Board will provide timely responses to questions from the training teams with responses available to all training personnel. This list of questions and responses will be recorded throughout the trial and used to refine or clarify issues in the training manual and on the ICARE website. The Clinical Site Coordinators will conduct routine on-site visits every month to each site and relay any intervention-related concerns to the Principal Investigators.

5.3 CONCOMITANT INTERVENTIONS

5.3.1 REQUIRED INTERVENTIONS

Since the possibility exists that following randomization, participants may seek additional or other treatments, we will monitor those options and acquire data on a monthly basis during the one year of participant commitment to ICARE. Acquiring this information is important, because additional physical or pharmacological treatments could impact changes in primary and secondary outcomes. Upon enrollment, each individual will be given a notebook containing a calendar notifying them of subsequent appointment dates. The notebook will also contain another calendar housing a check list including all interactions with any health care provider and all medications and devices. Antidepressant use is not an exclusion, but will be monitored for secondary analyses. All complications (including those which would have caused exclusion from the study had they occurred prior to randomization) and resulting treatments will be recorded, but such individuals will remain in the study because of the intent-to treat analysis plan. The calendar is constructed so that patients need only check the type of intervention and where relevant, the dosing. The information will be conveyed to site teams through monthly phone calls and scheduled re-evaluations. This procedure was employed successfully at the Emory EXCITE, and the USC Northstar EVEREST coordination sites. This is where we will monitor all drug therapies that we expect could be extensive based on our proof of principle data.

5.4 ADHERENCE ASSESSMENT

Tracking compliance during the intervention for those randomized to ASAP will be done at two levels: 1) compliance with the schedule of visits up to 30 hours and 2) compliance with out-of-laboratory action plans. The latter will be accomplished through a brief discussion at the beginning of the next visit regarding the “out-of-lab” action plan assignment and mitt use. The patient will be expected to report the results of their assignment and any mitt use and to keep a log of each during the intervention interval. In the unlikely event that participants fail to engage in action plan activities, we will compile reasons for such failures. Adherence to post-intervention action plans will be assessed during monthly phone calls at which time the interviewer will ascertain the extent to which each participant has continued and progressed the activities he/she determined at the end of the outpatient visits. In an effort to monitor out-of-therapy arm use for all groups, we will devise a check list that will be collected monthly (calendar format) during our follow-up calls to define amount of time estimated to have been spent

using the impaired arm daily. While fraught with problems regarding accuracy, it is the most “real” and cost effective way to do so. We will simply examine estimates of use over time. Intervention therapists will provide a rating of the extent of likely engagement of the participant in significant upper extremity practice outside the training setting as a function of the participant’s description of activities, identification of successes and barriers to be addressed, and demonstration of practiced movement behaviors. Patient self-reports of outside activity will also be obtained from all participants in each study arm through exit instruments.

6 CLINICAL AND LABORATORY EVALUATIONS

Evaluations are described in detail in Sections 2.H and 2.M of the ICARE Manual of Procedure.

6.1 PRIMARY OUTCOME MEASURE: WOLF MOTOR FUNCTION TEST (WMFT)

The Wolf Motor Function Test (WMFT)¹ determines the time required for patients with stroke to perform 15 everyday tasks with each upper extremity. Over the past 6 years, this measure has been used as either a primary or secondary outcome in at least 55 published studies. Performance time (up to 120 seconds), strength (in lbs for lifting and in kgs for hand grip), and quality of motor function based upon a 6-point scale Functional Activity Scale⁸⁸ are assessed. Tasks are sequenced so that the first seven tasks involve simple limb movements, primarily of the proximal musculature; the next ten tasks require manipulation and distal control. Many of the tasks are modified from the Jebsen-Taylor hand function test⁸⁹. Reliability for the Jebsen test was established by the original authors and grip strength reliability has also been reported by Mathiowetz and colleagues⁹⁰. The reliability and validity of this test are: inter-rater reliability - correlation coefficient > .80 and validity, $\pm 3\%$ accuracy for the Jamar dynamometer⁹⁰. Each WMFT task is defined by a specific, detailed “anchoring” definition. For each task, information regarding patient positioning, placement of objects to be targeted or manipulated, distance of the participant to the object, whether seated or standing, and verbal instructions have all been operationalized.

6.2 SECONDARY OUTCOME: MEASURE-SELF REPORTED PARETIC HAND FUNCTION – SIS HAND FUNCTION

The Stroke Impact Scale (SIS) is a full spectrum health status inventory. It is a stroke-specific, self-report measure composed of 59 items which are distributed in eight separate domains (strength, hand function, mobility, activities of daily living, emotion, memory, communication, and social participation). The SIS hand function domain is: 1) a valid and reliable measure that is well aligned with ICARE specific aims, 2) it has face validity for clinical meaningfulness, 3) we acquired estimates of the ‘natural’ change in SIS hand function during the acute and post-acute period when dynamic change is high and ICARE intervention occurs (Sec 4.3), and 4) this self-report measure of hand function corresponds well with our primary laboratory-based outcome of performance.

6.3 SECONDARY OUTCOME MEASURE: FULL SPECTRUM STROKE IMPACT SCALE

The full SIS will be administered at Baseline, Post-Intervention and both Follow-up evaluations. While the specific effects of the treatment intervention are expected to influence the hand function domain the most, we also expect several non-specific effects on health status generally and the composite physical performance and social participation domains contained in the full SIS. This was true for the EXCITE trial and we expect similar findings for ICARE.

6.4 OTHER SECONDARY OUTCOME MEASURES

A full battery of other measures will be taken at each evaluation point that will provide complementary information about muscle strength, functional ability, depression, self-confidence, life satisfaction, reintegration, and subjective quality of life. The specific tests are detailed in the MOP, but listed here for completeness under the International Classification of Function and Disability Framework⁹¹. **Body Function/Body Structure:** NIHSS, Arm Muscle Torque Test; WMFT (strength items); UE Fugl-Meyer (Motor); Patient Health Questionnaire-9 (PHQ-9); As-Tex Sensory Index; 20-item Confidence in Arm and Hand Movements (CAHM), Cognitive battery of (5) assessments to include: Short Blessed Memory Orientation Concentration Test, D-KEFS Verbal Fluency Test/Animal Naming, Hopkins Verbal Learning Test Revised (HVLTR), Color Trails Making Tests 1 & 2 and Digits Span Backward; Functional Independence Measure (FIM); and Monthly Follow-up Interviews

Activity: Motor Activity Log-MAL-28-QOM⁹⁸, EQ-5D. **Participation:** Reintegration to Normal Living Index (RNLI)^{99, 100}, Satisfaction with Life Scale (SWLS)¹⁰¹⁻¹⁰³, Single item subjective quality of life (SQOL)^{104, 105}, and Exit Interview.

6.5 SCHEDULE OF EVALUATIONS

We have selected measures that have established reliability and validity. A Table (MOP Table 2.M) of study measures, variables and data; protocol books for acquisition of measures; and data collection forms are in the Tests and Measures category of the MOP, Section 2.M. Staff blinded to group assignment will perform all evaluation measures. Evaluation therapists will generally be per diem (FFS) trained and certified clinicians (having passed the standardization certification), and are not part of the intervention teams. They will be unaware of treatment assignment and will conduct each baseline and follow-up assessment. The Site Coordinators will work with each participant to assure they are well-educated to refrain from discussing assignment group with the evaluator. All evaluation and follow-up measures will be performed at a different physical location than where the intervention will be administered, further reducing the risk of unblinding. To determine the effectiveness of our single blinded assessments, we will ask both the therapists and participants to complete a brief assessment to determine if group assignment was revealed during the evaluation. All incidents of unblinding will be documented as a protocol violation.

6.6 TIMING OF EVALUATIONS

This section includes definitions of the column headings in Table M.1, Schedule of Evaluations.

6.6.1 PRE-RANDOMIZATION EVALUATIONS

These evaluations occur prior to the participant receiving any study interventions. Enrollment procedures are described in detail in Section 2.H of the ICARE Manual of Procedure.

6.6.1.1 Pre-Screen (Express Chart Screen)

To determine initial eligibility, the Clinical Site Coordinator, Site Physician or other qualified site personnel will perform an Express Chart Screen (ECS) on all stroke patients admitted to participating facilities and their affiliated sites as well as direct referrals to the study. The Pre-Screen Reasons for exclusion will be recorded via ICARE Form PSF1 but no patient identifying information will be reported. Candidates who pass will be introduced to the study by the Clinical Site Coordinator, Site Physician or other qualified site personnel, provided a Screening Informed Consent and HIPAA Authorization to undergo a second screening assessment and requested to participate.

6.6.1.2 Screen (Brief & Detailed Clinical Screens)

Candidates who pass the Express Chart Screen will be introduced to the study by the Clinical Site Coordinator, Site Physician or other qualified site personnel. After a HIPAA Authorization and Screening Informed Consent are obtained, a Brief Clinical Screen will be initiated followed by a Detailed Clinical Screen. The Screen reasons for exclusion will be recorded and reported via ICARE Form SF11.

Candidates who pass the Detailed Clinical Screen will be provided a Study Informed Consent and Videotaping Informed Consent.

6.6.1.3 Baseline Evaluation

After full compliance with all inclusion and exclusion screening criteria, the Site Physician will perform a Brief Medical Exam (BME) and clear the participant to proceed to the Baseline Evaluation. The BME will include the NIHSS and PHQ-9, which recheck eligibility and also serve as baseline measures for later outcome analysis. If the BME occurs more than 72 hours prior to the Baseline Evaluation, an interceding stroke event will be ruled out by a licensed therapist or physician from the recruitment team prior to initiating the Baseline Evaluation. The baseline evaluation will proceed at no more than 106 days post-stroke.

The baseline evaluation consists of the primary outcome measure of the Wolf Motor Function Test (WMFT), Stroke Impact Scale (SIS) and secondary outcome measures that fall within the international classification system of Body Structure/Body Function, Activity and Participation. The full UE Motor Fugl-Meyer will be administered first at the Baseline Evaluation to confirm eligibility. Therefore, prior to randomization, participants will have completed the baseline evaluation and all relevant stratification variables

entered into the ICARE database via website. These will be summarized via ICARE Form EF16, which is auto-generated from the multiple source forms.

6.6.2 RANDOMIZATION

Randomization is described in detail in Section 2.H of the ICARE Manual of Procedure. Randomization will be done after the Baseline Evaluation is completed and eligibility is confirmed. Upon successful completion of the Baseline Evaluation, participants will be stratified and randomized to one of three intervention groups.

6.6.3 ON-STUDY EVALUATIONS

There are no formal evaluations for the purpose of outcome measures scheduled during the intervention period.

6.6.4 POST-INTERVENTION EVALUATIONS AND FINAL EVALUATION

There are three scheduled follow-up time points. The first will be performed immediately post intervention (approximately 126-246 days post stroke). The second follow-up evaluation (FU1) will occur at 6 months post randomization (182-303 days post stroke). The final follow-up evaluation (FU2) will be conducted 12 months post randomization (365-485 days post stroke). At the final evaluation (FU2) participants will be asked a set of questions that will provide manipulation checks or that address the extent to which each critical component of the intervention (e.g., interfering impairments, challenging workloads, participant chosen tasks, and self-efficacy) were incorporated in the assigned intervention¹⁰⁶. Participants will also be asked to report the perceived value of the intervention. At the 1-year time point, study exit questions will focus on overall impact of the study as well as participants' activity between the end of intervention and the end of the study.

6.7 SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS

The following is a brief description of the rows of the Table 6.1 Schedule of Evaluations.

6.7.1 EXPRESS CHART SCREEN, SITE IRB HIPAA WAIVER (PSF1)

All patients admitted or referred to a participating site or its affiliate with a diagnosis suggestive of vascular brain injury will undergo an Express Chart Screen review using the eligibility criteria found in Section 2.H of the ICARE MOP. A HIPAA Waiver has been obtained by the IRB of each participating site. These will permit the Express Chart Screen. If all of the exclusion criteria are passed, meaning that none are true, a Screening Informed Consent and HIPAA Authorization will be requested.

6.7.2 HIPAA AUTHORIZATION & SCREENING INFORMED CONSENT (IC1/IC2)

HIPAA Authorization, as can be found in [section 2.1](#) of the MOP, will be presented along with the Screening Informed Consent if the patient passes the Express Chart Screen. Each investigative clinical site's informed consent documents may vary slightly due to the requirements of each individual IRB. The Clinical Site Coordinator, Site Physician or other qualified site recruitment personnel will consent the potential participant. Please refer to Section 2.I of the ICARE MOP for a description of the informed consent process and to view the sample Screen Informed Consent and HIPAA Authorization.

Each investigative clinical site's informed consent documents may vary slightly due to the requirements of each individual IRB.

6.7.3 BRIEF CLINICAL SCREEN

The Brief Clinical Screen (BCS) is an additional check for exclusion via administration of 3-items of the NIHSS related to upper extremity function; Upper Extremity Fugl-Meyer (motor component); pre-morbid Barthel Index; and PHQ-2, as an early screen for depression. The specific exclusion items may be found in Section 2.H of the MOP. Participants who are not eligible at the initial BCS because they do not demonstrate enough recovery, may be followed prospectively at the discretion of the Clinical Site Coordinator and Site Physician.

6.7.3.1 NIH Stroke Scale (SF1 & EF2)

Please refer to the ICARE web-site for instructions on how to administer the NIH Stroke Scale and the evaluation form (CRF). In the Screening Phase, only items 1c, 7 & 8 will be administered to determine eligibility related to ability to follow motor command, ataxia and sensation. At Baseline and follow-up evaluations, all items will be administered.

6.7.3.2 UE Fugl-Meyer, motor component (UEFM) (SF8 & EF6)

The UE Fugl-Meyer motor section includes component tests of reflexes, active motion, and coordination. The motor section has a maximum score of 66 and measures reflexes, volitional movement including flexor/extensor synergies, movement combining synergies, movement out of synergy, stability and movement of wrist and hand, and coordination/ speed. Please refer to the ICARE web-site: www.icarestroke.org for instructions on how to administer the UE Fugl-Meyer (Motor) and the CRF. Participants who are not eligible at the initial UEFM administration because they do not demonstrate enough motor recovery, may be followed prospectively at the discretion of the Clinical Site Coordinator and Site Physician.

6.7.3.3 Barthel Index (SF2)

This is a measure of pre-stroke function. Please see the ICARE web-site for instructions on how to administer the Barthel Index and the evaluation form (CRF).

6.7.3.4 PHQ-2 (SF3)

Depression constitutes a secondary outcome of interest in the proposed ICARE study. Impact of the upper extremity interventions on depression will be measured with the 2-item self-report Patient Health Questionnaire-2 (PHQ-2), a truncated version of the PHQ-9¹⁰⁷⁻¹¹⁰, which is reflective of current DSM-IV and ICD-10 criteria for diagnosis of depressive disorders and developed to screen and diagnose depression in individuals in primary care settings. The PHQ-9 has been used in an NINDS-funded study⁹⁴ to screen for depression in the 1- to 3-month post-stroke interval (nearly identical to ICARE's 14-106 day post-stroke interval) and has been found responsive to treatments for depression in a multisite treatment trial of late-life depression⁹³. In the abbreviated PHQ-2 screen, respondents report the frequency (from 0, not at all, to 3, nearly every day) during the previous 2 weeks that he/she has experienced each of first 2 items of

the 9 depressive symptoms surveyed in the PHQ-9. Scores are summed to create a summary scale score that can range from 0 (no depressive symptoms) to 6 (both symptoms occurring nearly daily). The PHQ-2 will be administered during the brief clinical screening phase. The purpose of this early administration is to be able to detect possible indicators of depression for further work-up and intervention as the medical team deems appropriate. Hopefully, through early intervention, participant distress may be minimized and eligibility at time of baseline may be facilitated. The PHQ-9 will then be administered by the Clinical Site Physician or the Clinical Site Coordinator during the Brief Medical Exam, just prior to the Baseline Evaluation and randomization. This will be a final check for eligibility. Please see the ICARE web-site: www.icarestroke.org for instructions on how to administer the PHQ-2 and the evaluation form (CRF). A Study Psychologist is available on-call to the clinical site teams for consultation, should the need arise.

6.7.4 DETAILED CLINICAL SCREEN

If the Participant passes the BCS, a Detailed Clinical Screen (DCS) will follow. Specific inclusion/exclusion items to be covered during the detailed clinical screen include checks for Exclusion criteria via: Mesulam Star Cancellation test, Mini-Cog, participant interview and physical exam. The specific exclusion items checked may be found in Section 2.H of the MOP. Participants who are not eligible at the initial DCS because they do not demonstrate enough recovery, may be followed prospectively at the discretion of the Clinical Site Coordinator and Site Physician.

6.7.4.1 Pain & ROM Exam (SF5)

Upper Extremity Passive Range of Motion (PROM) and pain are assessed in a brief bedside physical exam to be performed by the Clinical Site Coordinator, Physician Investigator and/or other qualified designated personnel, during the Detailed Clinical Screen. Measurements are recorded as they relate to the eligibility criteria at screening.

6.7.4.2 Mesulam Unstructured (SF6)

The Mesulam Unstructured tests for neglect. It can be administered in about 3 minutes, requires no special equipment, and is relatively uninfluenced by level of education or language variations. Test administration instructions and source forms (SF6) are available on the ICARE web-site.

6.7.4.3 Mini-Cog (SF7)

This is a test of cognition in which the participant must recall 3 randomly assigned words following a distraction task of drawing a clock. Please see the ICARE web-site for instructions on how to administer the Mini-Cog and the evaluation form (CRF).

6.7.5 EXCLUSION CRITERIA CHECKLISTS (SF11 & EF16)

These are summary forms documenting eligibility after screening. There are (3) reference tables that serve as a guide to the clinical team to identify the eligibility criteria checked respectively at: Pre-Screening (Express Chart Screen (PSF1)); Screening (Exclusion Criteria Checklist at Screening (SF11)) and Baseline (Exclusion Criteria Checklist at Baseline (EF16)). For reporting purposes, there are (2) forms, autopopulated directly from the source documents used during Screening, that summarize the exclusion criteria checked during Screening (Form SF11) and Baseline (Form EF16). Please see Section 2.H of the MOP for the referenced tables and the ICARE web-site for the automated forms.

6.7.6 STUDY INFORMED CONSENT & CONSENT TO BE VIDEOTAPED (IC3/IC4)

If the Participant passes the Brief and Detailed Clinical Screens, The Clinical Site Coordinator, Site Physician or qualified Site Recruiter, will present the Study Informed Consent and Consent to be Videotaped and explain the study in more detail. Please refer to Section 2.I of the MOP for a description of the informed consent process and to view the Study Informed Consent document.

6.7.7 LETTER OF PARTICIPATION TO PRIMARY CARE PHYSICIAN (MR1)

Once the Participant signs the Study Informed Consent & Consent to be Videotaped, a letter describing the ICARE study will be sent to the prospective participant's primary care physician along with a HIPAA Authorization signed by the Participant. This will briefly explain the study and request cooperation sharing any medical information necessary to assure participant safety during participation in the research study, (e.g. weight-bearing precautions and blood pressure or heart rate parameters). Please refer to the ICARE web-site for an example of the letter.

6.7.8 ADDITIONAL DATA COLLECTION

If the Participant consents to the study, some additional data including a stroke characterization report, history and demographic report, FIM admission and discharge scores, and a Medical Release are obtained near the Baseline Evaluation.

6.7.8.1 Stroke Characterization (SF0)

The Stroke Characterization information is obtained from the medical record by the Clinical Site Coordinator, Physician Investigator and/or other qualified recruitment personnel. It provides relevant information about the instant stroke, co-morbidities and past medical history.

6.7.8.2 History & Demographic Interview (SF9)

These data are obtained via Participant interview by the Clinical Site Coordinator, Physician Investigator and/or other qualified recruitment personnel.

6.7.8.3 Functional Independence Measure (FIM) (SF4, SF10 & EF15)

The Functional Independence Measure (FIM) data are recorded 3 times during the ICARE trial. Both an admission FIM (SF4) and discharge FIM (SF10) are extracted from the medical chart (inpatient rehab FIM scores are preferred). At the 1 year post randomization evaluation, the FIM is again obtained via participant interview.

6.7.9 BRIEF MEDICAL EXAMINATION AT BASELINE (MR3)

The Brief Medical Exam is conducted by the Site Team Physician, or his/her qualified proxy, just prior to Baseline and serves as a re-check for a) severe depression absent a management plan, via PHQ-9; b) neurological decline, via the NIH Stroke Scale and physical exam; c) medical stability, via physical exam and d) concurrence with screening findings. Results are reported via MR3 and provide a final release to proceed with baseline testing and participation in the study. If at the Baseline Evaluation, more than 72 hours have passed since the Brief Medical Exam, a licensed recruiting therapist or the site physician will confirm the absence of a new neurological event by asking the following (2) questions:

- 1) Have you had any spells in the last (insert interceding time) that you thought were a stroke?
- 2) Have you seen your doctor or been to a hospital for an unplanned visit in the last (insert interceding time)?

If either question is answered with a "YES", then the Participant must be cleared by the Site MD before proceeding with the Baseline Evaluation.

6.7.10 PARTICIPANT SAFETY & CONTACT INFORMATION (CS01)

ICARE Form CS01 is for internal site use only. It contains:

1. Participant Contact Information;
2. Emergency Contact Information;
3. Medications;
4. Co-Morbidities;
5. Medical Concerns and Parameters (as reported by the Site Physician at the Brief Medical Exam and those provided by the Primary Care Physician)
6. Physician Contact Information;
7. Transportation Contact Information

The Clinical Site Coordinator is responsible for assuring that CS01 is maintained with current data and is available to both Blinded Evaluators and ASAP Therapists at every participant contact.

6.7.11 PRIMARY OUTCOME MEASURE

6.7.11.1 Wolf Motor Function Test (WMFT) – Time (EF3 & EF3a)

This test consists of 17 items, 15 of which involve timed performance on various tasks; these comprise the primary outcome measure for the ICARE trial. Tasks are sequenced by complexity and the number of joints primarily responsible for task completion. The

first seven tasks involve simple limb movements, primarily of the proximal musculature; the next ten tasks require manipulation and distal control. Performance time (up to 120 seconds) is measured. For Spanish language participants, a standardized bilingual therapist must administer the WMFT; a translator is not permitted. Please see the ICARE web-site for instructions on how to administer the WMFT and the evaluation form (CRF).

6.7.12 SECONDARY OUTCOME MEASURES: BODY STRUCTURE/BODY FUNCTION

Body Structure/Body Function is one domain within the International Classification System.

6.7.12.1 Arm Muscle Torque Test (EF8)

Maximum isometric torque will be tested for six isometric positions using the hand held Lafayette MMT digital dynamometer, model #01163, and standard testing positions. The MMT test consists of isometric “make contractions” in which the patient uses each tested muscle group to push maximally against the curved plate and the piston of the hand-held device for 4-5 seconds. Each muscle group will be tested three times and the highest score will be used. Please see the ICARE web-site for instructions on how to administer the Arm Muscle Torque Test and the evaluation form (CRF).

6.7.12.2 WMFT- Strength Items (EF3a)

2 items of the WMFT measure strength - in lbs for lifting, and in kgs for hand grip. Please see the ICARE web-site for instructions on how to administer the WMFT and the evaluation form (CRF).

6.7.12.3 UE Fugl-Meyer (Motor) (EF6)

The UE Fugl-Meyer (UEFM) motor section includes component tests of reflexes, active motion, and coordination. The motor section has a maximum score of 66 and measures reflexes, volitional movement including flexor/extensor synergies, movement combining synergies, movement out of synergy, stability and movement of wrist and hand, and coordination/ speed. Please refer to the ICARE web-site for instructions on how to administer the UEFM and the CRF.

6.7.12.4 PHQ-9 (EF1)

Depression constitutes a secondary outcome of interest in the proposed ICARE study. Impact of the upper extremity interventions on depression will be measured with the 9-item self-report Patient Health Questionnaire-9 (PHQ-9) ¹⁰⁷⁻¹¹⁰ reflective of current DSM-IV and ICD-10 criteria for diagnosis of depressive disorders and developed to screen and diagnose depression in individuals in primary care settings. Respondents report the frequency (from 0, not at all, to 3, nearly every day) that they have experienced each of 9 depressive symptoms during the previous 2 weeks. Scores are summed to create a summary scale score that can range from 0 (no depressive symptoms) to 27 (all symptoms occurring nearly daily). A minimal clinically important difference for individual change has been established as 5 points on the 0 to 27 point PHQ-9 scale ⁹³. The

PHQ-9 will be administered by the Clinical Site Physician or the Clinical Site Coordinator during the Brief Medical Screen of the Baseline Evaluation, just prior to randomization. This will be a final check for eligibility. As described in Section 6.3.11, the PHQ-2 will have been administered earlier, during the Brief Clinical Screen, with the goal of detecting indicators of depression early on and thereby permitting adequate time for further work-up and intervention as the medical team deems appropriate. Hopefully, through early intervention, participant distress may be minimized and eligibility at time of baseline may be facilitated by remedying depressive signs & symptoms early in the screening phase. As a secondary outcome measure, the PHQ-9 will be re-assessed by the Blinded Evaluator immediately post-intervention, at 6 months post randomization, and at the 1-year post-randomization assessment. Please see the ICARE web-site for instructions on how to administer the PHQ-9 and the evaluation form (CRF). A Study Psychologist is available on-call to the clinical site teams for consultation, should the need arise.

6.7.12.5 Confidence In Arm And Hand Movements (CAHM) (EF12)

The 20-item Confidence in Arm and Hand Movements ¹¹¹ scale was designed to examine self-efficacy or confidence for arm and hand function in individuals following stroke in home (e.g., “How certain are you at the present time that you can open a large-mouth jar?”) and community or public contexts (“How certain are you at the present time that you can cut food with a knife and fork at a restaurant?”). Items refer to unimanual and bimanual activities and are scored on a 0 (very uncertain) to 100 (very certain) scale and averaged to provide a total score ranging from 0 to 100. Preliminary evidence of instrument reliability and validity is strong. Please see the ICARE web-site for the instructions on how to administer the CAHM and the evaluation form (CRF).

6.7.12.6 Astex Sensory Index (EF9)

The AsTex® is a quick, accurate and reliable tool for assessing sensation of the hand.^{148, 149} In the ICARE study, the AsTex® screening instrument will be utilized to assess hand sensation at the baseline, immediately post-intervention, 6- and 12-months post-randomization time points. The index finger of each hand is tested separately. After a practice test with each index finger, the blindfolded subject runs the pulpa of the digit across the screening instrument from the rough end toward the smooth end and stops when smoothness is first detected. The mean of 3 trials for each digit is converted from a raw distance measure into a texture discrimination index (TDI) score, which may be then examined for change comparison within subjects across time or related to age-adjusted normative values to detect sensory impairment. Please see the ICARE web-site: www.icarestroketrial.org for instructions on how to administer the Astex and the evaluation form (CRF).

6.7.12.7 5-item Cognitive Battery (EF5a-e)

A 5-item cognitive battery of assessments will be administered at baseline and the 1-year post randomization assessment. These secondary outcome measures were adopted by the ICARE study team during the Year 1 start-up. Upon recognizing the multiple cognitive demands inherent to the investigational protocol, the ICARE

investigative team felt that a baseline cognitive measure was important for later covariate analysis. The 5 tests identified include: Short Blessed Memory Test, D-KEFS Verbal Fluency Test, HVLT-R Hopkins Verbal Learning Test Revised, Digits Span Backwards and Color Trails Making Tests 1 & 2. For the specific administration instructions and clinical source forms to be used in the ICARE study, please go to the ICARE web-site.

6.7.13 SECONDARY OUTCOME MEASURES: ACTIVITY

Activity is a domain within the International Classification System.

6.7.13.1 Stroke Impact Scale, version 3.0 (EF4)

The Stroke Impact Scale (SIS) is a full spectrum health status inventory. It is a stroke specific, self-report measure composed of 59 items which are distributed in eight separate domains (strength, hand function, mobility, activities of daily living, emotion, memory, communication, and social participation). The SIS hand function domain is: 1) a valid and reliable measure that is well aligned with ICARE specific aims, 2) it has face validity for clinical meaningfulness, 3) we acquired estimates of the 'natural' change in SIS hand function during the acute and post-acute period when dynamic change is high and ICARE intervention occurs, and 4) this self-report measure of hand function corresponds well with other laboratory-based measures of performance. Please see the ICARE web-site for instructions on how to administer the SIS and the evaluation form (CRF).

6.7.13.2 WMFT Functional Ability Scale (FAS) (EF3b)

Quality of movement based upon a 6-point scale Functional Activity Scale⁸⁸ (FAS) are assessed. Please see the ICARE web-site for instructions on how to administer the WMFT and the evaluation form (CRF).

6.7.13.3 MAL-28 (QOM) (EF10)

MAL-28-QOM a structured interview intended to examine how well the participant uses the more affected arm outside of the laboratory setting. Participants are asked 28 standardized questions about the quality of their movement during the functional activities indicated ("How Well" Scale or HW). Please see the ICARE web-site for instructions on how to administer the MAL-28 (QOM) and the evaluation form (CRF).

6.7.13.4 Functional Independence Measure (FIM) (SF4, SF10 & EF15)

See Section 6.7.8.3 of this Protocol for details.

6.7.14 SECONDARY OUTCOME MEASURES: PARTICIPATION

Participation is a domain within the International Classification System.

6.7.14.1 Reintegration To Normal Living Index (RNLI) (EF13)

The Reintegration to Normal Living Index (RNLI) was designed for use in follow-up assessments of individuals with a limiting physical or cognitive condition. The goal of this scale is to help document how a person is able to resume normal life activities after an incapacitating injury or illness. The RNL assesses global function and measures the

individual's satisfaction with basic self-care, in-home mobility, leisure activities, travel and productive pursuits. Individuals respond to 11 statements used to assess reintegration into their pre-insult pattern of living. The scale has high internal consistency and interrater reliability. Construct, content and predictive validity have also been established. This assessment is based on an 11-55 total score range, wherein a lower score indicates a higher attainment of normal levels of living. Please see the ICARE web-site for instructions on how to administer the RNLI and the evaluation form (CRF).

6.7.14.2 Satisfaction With Life Scale (SWLS) (EF7)

The Satisfaction with Life Scale (SWLS) ¹⁰² is a 5-item scale that assesses participants' overall life satisfaction without explicit reference to particular domains such as health, activities, or role-related functioning (e.g., "The conditions of my life are excellent."). Responses to each item can range from 1 = strongly disagree to 7 = strongly agree. The SWLS has demonstrated validity and reliability and has been used in a variety of patient and non-patient samples ^{101-103, 112}. Higher scores indicate higher perceived life satisfaction. Please see the ICARE web-site for the evaluation form (CRF).

6.7.14.3 Single Item Subjective Quality Of Life (SQOL) (EF14)

The Subjective Quality of Life measure ¹⁰⁵ is a single-item rating of participant perception of overall quality of life, distinct from satisfaction with life or explicit health-related quality of life. Respondents rate their quality of life on a visual analogue scale anchored by the phrase "Life is very distressing" on the low end, "Life is great" on the high end and "Life is so-so" in the middle. This measure has been used in several studies of individuals with disabilities from a variety of diagnoses ^{104, 113}. Please see the ICARE web-site for the evaluation form (CRF).

6.7.14.5 End Of Study Exit Interview (EF19)

At the 1-year time point, study exit questions will focus on overall impact of the study as well as participants' activity between the end of intervention and the end of the study. Participants will also be asked to report the perceived value of the intervention. Please see the ICARE web-site for the evaluation form (CRF).

6.7.14.6 EQ-5D (EF11)

The EQ-5D is a widely used, 3-level (none, some/moderate or extreme problems), 5-dimensional (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) standardized assessment, designed for participant self-report of health status.¹⁵⁰

Administration is quick and simple and it is recommended for use in cost-effectiveness analyses by the Washington Panel on Cost Effectiveness in Health & Medicine.¹⁵⁰ In the ICARE study, it will be administered at baseline, immediately post-intervention, 6- and 12- months post-randomization. *(After revision, the MOP will contain specific detail on the administration and CRF's for this test instrument.)*

6.7.15 SECONDARY OUTCOME MEASURES: COMPREHENSIVE OF BODY STRUCTURE/FUNCTION, ACTIVITY AND PARTICIPATION

Comprehensive of all domains within the International Classification System.

6.7.15.1 Stroke Impact Scale (SIS) (EF4)

See section 6.3.15.1 above for a description of the SIS.

6.7.16 NON-OUTCOME MONITORING

6.7.16.1 Physiologic Measures

Vitals including blood pressure and heart rate are taken at each evaluation, and for those in the investigational arm of the trial, at each intervention visit. Physiologic measures are recorded on the respective evaluation or daily intervention forms. Please see the ICARE web-site for the evaluation form (CRF).

6.7.16.2 Immediate Post Intervention Exit Interview (EF17)

A multiple question survey Interview will be administered after the end of the therapy phase. At the post-intervention assessment, participants will be asked a set of questions to provide manipulation checks or that address the extent to which critical components of interventions (e.g., interfering impairments, challenging workloads, participant chosen tasks, self-efficacy) were incorporated in the assigned intervention

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6.7.16.3 Monthly Follow-up Interviews (EF18)

Beginning 30 days following randomization, the recruiting site team will conduct a monthly interview of the participant by telephone to ascertain information/changes about: health status; healthcare utilization; medications; other therapies; and adverse events. Please see the ICARE web-site for the evaluation form (CRF) and scripting for this interview.

6.4 OFF-INTERVENTION REQUIREMENTS

There are no specific requirements for follow-up once Participants have completed the study intervention besides attending the post-randomization, 6 month post and 12 month post follow-up evaluations. There will be monthly follow-up phone interviews to document any changes in medical status, hospital and doctor visits, other therapies, and change in medications

7. MANAGEMENT OF ADVERSE EXPERIENCES

For details regarding identification and management of adverse events, please refer to Section 2.P of the ICARE Manual of Procedures.

8 CRITERIA FOR INTERVENTION DISCONTINUATION

Death: Official written confirmation. Resolution procedure: None, lost to intention to treat or to follow-up.

Relocation: Confirmation from caregiver/family member that participant is moving far enough away from site location as to preclude continued participation or availability for follow-up evaluations. Resolution procedure: Attempt to convince family to stay until end of intervention and to return for scheduled follow-up evaluations.

Hospitalization: Confirmation from caregiver/family member that participant has been hospitalized to the extent that ≥ 4 consecutive weeks of intervention will be lost, or that treatment may not be completed within the maximally allowed 16 weeks, or follow-up evaluations cannot be undertaken within one month of scheduled date. Resolution procedure: None, lost to intention to treat or to follow-up.

Absence: Caused by prolonged illness, unanticipated travel, or loss of transportation to the extent that ≥ 4 consecutive weeks of intervention will be lost, or that treatment may not be completed within the maximally allowed 16 weeks, or follow-up evaluations cannot be undertaken within one month of scheduled date. Resolution procedure: None, lost to intention to treat or to follow-up.

Non-compliance/conflict: The emergence of family conflict or combative interactions that preclude to attend therapy 3 days a week for the out-patient program, and attend follow-up sessions up to 12 months later. Resolution procedure: Attempt to work with family to assure compliance to behavioral contract and improved communication options.

Discovery of incorrect diagnosis: Caused by observations from re-read of neuroimages or other information provided subsequent to enrollment. Resolution procedure: None, lost to intention to treat or to follow-up.

9 STATISTICAL CONSIDERATIONS

PLEASE REFER TO THE STATISTICAL ANALYSIS PLAN FOR THIS INFORMATION

10 DATA COLLECTION, SITE MONITORING AND ADVERSE EXPERIENCE REPORTING

Please refer to the Statistical Analysis Plan and sections 2.P and 2.T for this information.

10.1 RECORDS TO BE KEPT

Participants' research records including all demographic information, contact information, assessment data and training data will be kept confidential by the investigators to the extent permitted by law. Specific study-related information may be sent to the sponsor, who is the National Institutes of Health, but the participants' names will be deleted.

Every effort will be made to keep the participants' personal information confidential. Personal-identifying data will be stored in locked files and in password-protected computer accounts to ensure confidentiality. Only staff that is processing these data for Institutional Review Board (IRB)-approved research studies will have access to the information. We cannot guarantee absolute confidentiality. Participants' personal information may be disclosed if required by law. The information from this study may be

published in scientific journals or presented at scientific meetings, but the participants' identity will not be revealed.

If photographs, videos, or audiotape recordings of the participants will be used for educational purposes, the participants' identities will be kept confidential. The participants may review the tapes if they wish and obtain a copy if they would like. The research team will have access to these tapes for data analysis purposes. After the data analysis is complete, the tapes will be destroyed.

10.2 ROLE OF DATA MANAGEMENT

10.2.1 CLINICAL SITE RESPONSIBILITIES

Each clinical site will be responsible for all data collection and data management for the participants they recruit. Data management includes storage, security and confidentiality as discussed above, and data entry. Therefore, each site will enter the data using web-based entry designed and managed by the Data Management Center at USC (see below for details).

10.2.2 THE DATA MANAGEMENT CENTER (DMC)

The Data Management Center (DMC) is housed at the Statistical Consulting and Research Center (SCRC), Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA.

The DMC responsibilities in data management include providing expertise for multi-center studies in all aspects pertaining to the development and operation of the randomization process, website and database design, data quality checking, study reports and data analysis.

Please see Section 2 of the Statistical Analysis Plan (SAP) and Section 2.C of the ICARE MOP for details regarding the DMC specific aims, roles and responsibilities.

10.3 QUALITY ASSURANCE

Data will be checked for integrity and verification. The remote data entry component will include online error checking, based on range checks or relational checks. To ensure quality data, pre-programmed range checks will be defined in the data dictionary and built into the web-based data entry system. An error report page (when errors occur) will be interactively returned to the user. Once corrections are completed, a 'verified screen' will appear and it will be the user's responsibility to verify that the data about to be submitted are correct, thereby offering the user an opportunity to make additional corrections before submission. Variables defined as required will not allow blanks to be entered. Based on our past experience, a data element will not be collected unless it meets one of the following needs: study objective; confirm eligibility; government regulatory information; assessment of safety; quality assurance. By limiting the scope of data collected to essential elements, the net effect will be to have high quality data. One reason is that those responsible for collecting the data will have the necessary time to collect and check the most critical data elements. Security will be flexible enough to

monitor access down to the data field level. The database will track who made the transaction and the time and date of the transaction for each successful data submission. Every successful submission of a transaction will be recorded in on-line archive tables, this providing a complete audit trail of data/form changes and/or modifications. That is, the database can be recreated to any point in time. The analytic computer will contain snapshots of the data at specific times, including a current copy. Remote users will not conduct any direct transactions on the analytic databases.

In addition to the database records, each site will keep all hard-copy records and Standardized Case Report Forms (CRFs) available for inspection by the Site PI. Standardized Case Report Forms will be provided for use at the investigational sites through download from the Manual of Procedures. Investigators are responsible for completion and timely submission of the data to the DMC for data processing. Quality assurance procedures are designed to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed, and that complications and adverse device effects are reported. Incoming data are reviewed to identify inconsistent or missing data and adverse effects. Data problems will be addressed in calls and/or emails to the investigational site and during site visits by the Executive committee member. All hard copy forms and electronic data files will be secured to ensure confidentiality. Please see Section 8 of the SAP for further details about Quality Monitoring and Assurance.

10.4 ADVERSE EXPERIENCE REPORTING

A data safety monitoring board has been established by the NINDS to monitor the well being of the study participants, ensure scientific integrity of the study and assure timely participant accrual. The Physician Investigators at each site are responsible for reviewing the activities of the clinical trial including reporting all adverse events at his/her site within 24 hours of site team notification of the event and reviewing incidence and type of adverse events across the study. Each Physician Investigator will also consult with Dr. Alex Dromerick, a board-certified Neurologist and Principal Investigator of the trial, relative to complications and questionable progression of participants during the intervention period.

All serious adverse events will be reported immediately to the DSMB liaison and each sites' IRB according to their respective protocol. The University of Southern California has established definitions for adverse events, criteria for causal relationships, and an adverse event protocol. These definitions and protocols will be used for reporting all adverse events from all sites for this study. During the course of the study, adverse events will be immediately entered into our database, and the DMC will generate an adverse event report that will be sent to the Data Safety Monitoring Board, the USC Administrative Site, and all site investigators. A cumulative adverse event reporting table will be completed for annual continuing review as well as any interceding intervals directed by the ICARE DSMB.

The DMC statistical core will check the data monthly for data safety monitoring variables that may lead to a 'stop' of the study. Every six months, we will prepare an institutional performance monitoring report, part of which will be on data timeliness, accuracy, and completeness scores. We will also give projections for each site of the scheduled completion dates for accrual, based on the actual accrual. In addition to the monthly data monitoring reports, participant accrual will be monitored weekly by site using a graphical plot of actual vs. planned accrual along with an accumulated enrollment by month for each site. These reports will be sent by email first to the Project Manager for verification, and once verified, sent out to all sites and posted on the secure reports page of the ICARE web site. We have found this procedure to be very effective in helping to meet expected participant accrual for our clinical research network, PTClinResNet and plan to use a similar procedure for ICARE. Please see Section 2.P of the MOP and Section 10 of the SAP for additional details regarding adverse event reporting.

11 HUMAN SUBJECTS

11.1 INSTITUTIONAL REVIEW BOARD (IRB) REVIEW AND INFORMED CONSENT

This protocol and the informed consent documents (Section 2.I of the MOP) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed Screening Informed Consent form and HIPAA Authorization will be obtained from the participant to determine eligibility. If the potential participant is a candidate, they will be asked to sign a Study Informed Consent that will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Potential participants are given ample opportunity to ask questions about the study. Participants who cannot consent for themselves are excluded from participation in this study. A copy of the consent form will be given to the participant or legal guardian/caretaker, and this fact will be documented in the participant's record.

11.2 PARTICIPANT CONFIDENTIALITY

Participant confidentiality will be maintained with all data records noting a code number and will be stored in a locked cabinet in the laboratory. All data will be password protected. Any evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain participant confidentiality. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee. Please also refer to Section 14 of the SAP for additional detail.

11.3 STUDY MODIFICATION/DISCONTINUATION

The study may be modified or discontinued at any time by the IRB, the NINDS, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected. Please see Section 13 of the SAP for additional detail.

12 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NINDS prior to submission.

13 REFERENCES

Please refer to the end of the Manual of Procedures (MOP) for a complete listing of all references, Section 4.0.

ICARE MANUALS OF PROCEDURE – REVISIONS TABLE					
#	MANUAL CHANGED	SECTIONS IMPACTED	CURRENT/REVISED PROCEDURE	PRIOR PROCEDURE	RATIONALE
1.	ALL	Rosters, PR & MOP 2.B, 2.C	Updated to reflect current staff as of 3/3/09	N/A	Accuracy
2.	ALL	Headers	Updated in top right to provide document name, last edit date & time stamp		Increased ease in identifying updated versions by providing real time measure
3.	ALL	Study Acronym	ICARE	I-CARE	Removed hyphen creating a 5-character acronym to match the 5 digits of the hand
4.	ALL	Grant #	1U01NS056256-01A2	R01xxxxxx	Changed to a U grant from NIH
5.	PR & MOP	Outcome Assessments – Secondary Measures (Multiple Sections)– Précis, Study Flow Diagram, PR Table 6.1, MOP Table 2.M.1	Add a Cognitive Evaluation to occur at Baseline & 1 yr follow-up. Specifically: Short Blessed Memory Orientation Concentration Test D-KEFS Verbal Fluency Test/Animal Naming HTLV-Total and Delay Recall Trail Making Test A Trail Making Test B WMS-III Digit Span Backward Neuropsychiatric Inventory Questionnaire	No Cognitive Evaluation among Outcome Assessments	The experimental protocol, ASAP, engages the participant in active self-reflection & problem-solving related to movement dysfunction. Due to this significant cognitive demand, the ICARE study team feels that baseline cognition is likely to impact outcome and therefore should be assessed to allow for covariate analysis. Although it is not anticipated that the ASAP protocol will improve cognitive function, the study team would like to reassess at 1yr post randomization to preserve the opportunity to analyze these data.

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ICARE MANUALS OF PROCEDURE – REVISIONS TABLE					
#	MANUAL CHANGED	SECTIONS IMPACTED	CURRENT/REVISED PROCEDURE	PRIOR PROCEDURE	RATIONALE
6.	PR & MOP	UCC Treatment Period (multiple sections) PR Précis, 8	UCC = 0-16 weeks, without interruption > 4 weeks	UCC – 1 st “epoch of care” defined as the max length of the 1 st prescription	The previous definition was felt to be too broad. Under the current definition, the treatment may extend to 16 weeks (max allowed for the other 2 groups), as long as there is not a lapse in treatment greater than 4 weeks. This was thought to account for potential interruptions waiting for insurance authorization, interruption for personal reasons, etc.
7.	PR & MOP	DEUCC Treatment Period (multiple sections) PR Précis, 8	DEUCC = 10 – 16 weeks, without interruption > 4 weeks	10 weeks	10 weeks is still the desired length of treatment, but it was recognized while collecting pilot data that greater flexibility was needed to allow for delays that may be caused by: waiting for ins. auth, personal reasons, staffing, etc.
8.	PR & MOP	ASAP Treatment Period (multiple sections) PR Précis, 8	ASAP = 10 – 16 weeks, without interruption > 4 weeks	10 weeks	10 weeks is still the desired length of treatment, but it was recognized while collecting pilot data that greater flexibility was needed to allow for delays that may be caused by: personal reasons, staffing, illness, etc.

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9.	PR& MOP	DEUCC & UCC Intervention Documentation Burden, Précis, PR 5.1.3	UCC & DEUCC Therapists will have no documentation burden. CSC's will have access to the outpt OT treatment record, will complete a minimal amount of documentation and monitor treatment	UCC & DEUCC Therapists would document treatment on uniform study forms	The ICARE investigative team was concerned that imposing a uniform documentation requirement upon the UCC & DEUCC therapists would potentially influence their care; thus all documentation requirements have been removed from these therapists
10.	PR, MOP & CRF	Screening for Exclusion & Eligibility Checks (multiple sections), Study Flow Diagram, PR 6.2	Reordered Inclusion-Exclusion Criteria and developed multiple phase screening protocol to progressively narrow eligible pool based on inclusion/exclusion criteria. Phases are: Pre-Screening (ECS) & Screening (BCS & DCS) Medical Screen (MSB) & Baseline Eval (FCE)	No protocol/order specified with Screening. Separate Inc/Exc lists existed with random ordering, i.e. no combining of like items.	Exclusion Criteria & Screening Assessments were reorganized to promote efficiency in determining eligibility; thereby minimizing burden to Participant & Site Team, while conserving resources & budget.
11.	PR, MOP & CRF	Exclusion Criteria: ECS #1 (multiple sections), PR 4.1.3,	A diagnosis of ischemic stroke or intraparenchymal hemorrhage (without intraventricular or subarachnoid extension) has not been made within the last 75 days.	No diagnosis of ischemic stroke or intraparenchymal hemorrhage (without intraventricular or subarachnoid extension) within the last 75 days.	Revised language to assist clinical Site Teams is identifying Pass v. Not Passed

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12	MOP & CRF	Exclusion Criteria: ECS #1b (multiple sections)	Added ECS #1b to collect data on specific reasons that a Participant did not pass ECS #1 (above)	None	In anticipation of possible need to augment recruitment, it is desirable to have statistical data on the types of stroke that are excluded under ECS#1 so that investigators may make educated decision in consideration of altering Inclusion/Exclusion criteria
13	PR, MOP & CRF	Exclusion Criteria: ECS #2 re: Prior Therapy (multiple sections)	May have had ≤ 2 Outpt OT visits	No prior therapy was permitted	In examining alternate recruiting sources during the start-up phase, direct referral was recognized as a likely & viable source. Most direct referrals are expected to come arise from outpt settings, and thus it is likely that participants from such a source may have had exposure to prior therapy. We want to keep this to a minimum. (2) visits allows for an evaluation and 1 treatment session prior to enrollment in ICARE.
14	PR, MOP & CRF	Exclusion Criteria: ECS #12 (multiple sections)	Extended to 12 mos	6 mos	Investigative team felt that extending window to a 12-month period would result in greater likelihood of detecting a problem with alcohol and/or drug abuse
15	PR, MOP & CRF	Exclusion Criteria: ECS #14(multiple sections)	Participant demonstrates evidence of a stroke affecting both sides	None	Added in order to r/o subjects presenting with bilateral deficits, but still allowing subjects with a “bilateral” stroke – such as brainstem/cerebellar

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#	MANUAL CHANGED	SECTIONS IMPACTED	CURRENT/REVISED PROCEDURE	PRIOR PROCEDURE	RATIONALE
16	PR, MOP & CRF	Exclusion Criteria: ECS #15, 15a, 15b (multiple sections)	Participant may not be involved in another study in conflict with ICARE	None	Excludes potential subjects that are involved in studies that may influence motor outcomes, while permitting involvement in non-conflicting studies, i.e. imaging, observational, etc.
17	PR, MOP & CRF	Exclusion Criteria: ECS #16 (multiple sections)	Participant is on excluded medication, DILANTIN, and is not reasonably expected to be off such medication by study baseline evaluation.	None	The medications in ECS #16-21 were identified during our July training workshop as potentially impacting motor outcomes, and thus, a decision was made to exclude them during the ICARE trial. Additionally, in an effort to maximize eligibility potential, we will screen for them early, thereby providing an adequate time period before baseline during which the patient and medical management team may consider alternatives if participation in the study is desired.
18	PR, MOP & CRF	Exclusion Criteria: ECS #17 (multiple sections), PR 4.2.5	Participant is on excluded BENZODIAZEPINE medication, and is not reasonably expected to be off such medication by study baseline evaluation.	None	See Above (line #16)
19	PR, MOP & CRF	Exclusion Criteria: ECS #18 (multiple sections), PR 4.2.5	Participant is on excluded medication, HALDOL, and is not reasonably expected to be off such medication by study baseline evaluation.	None	See Above (line #16)

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20	PR, MOP & CRF	Exclusion Criteria: ECS #19 (multiple sections), PR 4.2.5	Participant is on excluded PHENOBARBITOL medication, and is not reasonably expected to be off such medication by study baseline evaluation.	None	See Above (line #16)
21	PR, MOP & CRF	Exclusion Criteria: ECS #20 (multiple sections), PR 4.2.5	Participant is on excluded ANTISPASTICITY medication, and is not reasonably expected to be off such medication by study baseline evaluation	Was previously excluded, but without an offered remedy	See Above (line #16)
22	PR, MOP & CRF	Exclusion Criteria: ECS #21(multiple sections), PR 4.2.5	Participant is on excluded medication, RITALIN, and is not reasonably expected to be off such medication by study baseline evaluation. <i>(Form PSF1)</i>	None	See Above (line #16)
23	PR, MOP & CRF	Exclusion Criteria: DCS #42 (multiple sections)	Test changed to Mesulam Unstructured and scoring criteria changed to: asymmetry >3 = not passed	Star Cancellation	Test was changed to Mesulam Unstructured based on input from Alex Dromerick use of the same in past/present studies with which he has direct experience – Protect DC & VECTORS. This change was just made this week (3/2/09) and is still being fleshed out by our study psychologist.

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#	MANUAL CHANGED	SECTIONS IMPACTED	CURRENT/REVISED PROCEDURE	PRIOR PROCEDURE	RATIONALE
24	PR, MOP & CRF	Exclusion Criteria: DCS #45-51 re: Fugl-Meyer (multiple sections) PR 6.3.8, 6.3.15.3	Fugl-Meyer during inpt rehab screening reduced to 7 key upper extremity motor items; Full UE Motor exam remains at Baseline	Entire UE Motor Fugl Meyer during Screening and again at Baseline	Changed Fugl-Meyer, UE motor screening protocol at DCS level to 7 key items identified in Hsieh paper and 2-day workshop exploring role of Fugl-Meyer motor assessment in Research and Clinical Evaluation. Reduces burden to participant and clinical site team. Full UE motor battery preserved as baseline & outcome measure. Baseline measures will serve as final check for eligibility
25	PR, MOP & CRF	Exclusion Criteria: BCS #26 & FCE #31 re: PHQ (multiple sections) PR 6.3.11, 6.3.15.4	PHQ2 administered during BCS as early screen for possible intervention; PHQ9 administered by Site MD or CSC at Medical Exam at baseline as final chk for eligibility	Unclear	The PHQ-2 will be administered during the brief clinical screening phase, early in the inpatient rehab stay. The purpose of this early administration is to be able to detect possible indicators of depression for further work-up and intervention as the medical team appropriate. Hopefully, through early intervention, participant distress may be minimized and eligibility at time of baseline may be facilitated. The PHQ-9 will then be administered by the Clinical Site Physician or the Clinical Site Coordinator during the Medical Screening component of the Baseline Evaluation, just prior to randomization. This will be a final check for eligibility.

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#	MANUAL CHANGED	SECTIONS IMPACTED	CURRENT/REVISED PROCEDURE	PRIOR PROCEDURE	RATIONALE
26	PR, MOP & CRF	Exclusion Checklist at Baseline (multiple sections) PR 6.2	Added a Final Check for Eligibility at Baseline	None	Due to highly dynamic period during screening, 1-3 mos. post-stroke, and possibility of up to 21 days between detailed clinical screen and baseline eval; baseline measures have been enhanced to include a brief medical screen by site MD to check that no new neurological event has occurred, as well as recheck of several exclusion criteria. For specifics see: Reference Document: Exclusion Checklist at Baseline.
27	PR, MOP & CRF	Exclusion Checklist at Baseline: #32 (multiple sections)	Have you reasonably ruled out an interim stroke within the last 2 weeks?	None	See above (line #24)
28	PR, MOP & CRF	Outcome Assessments (multiple sections), PR Table 6.1, MOP Table 2.M.1, PR 6.2	No TEMPA	TEMPA	Overly burdensome cost outweighs benefit in light of WMFT already administered as primary outcome assessment
29	PR	9	Updated protocol and created separate Statistical Analysis Plan (SAP) See for details	See MOP of 8/21/07	Updated in accordance with requests from DSMB

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30	PR	10	Updated protocol and created separate Statistical Analysis Plan (SAP) See for details	See MOP of 8/21/07	Updated in accordance with requests from DSMB
31	PR	11	Updated protocol and created separate Statistical Analysis Plan (SAP) See for details	See MOP of 8/21/07	Updated in accordance with requests from DSMB
32	PR	Section 2: Table 2.2.4	Table inserted	No table	Table was inadvertently dropped from previous submission
33	PR	Section 2: Table 2.2.5	Table inserted	No table	Table was inadvertently dropped from previous submission
34	PR	Section 3: Figure 3.1.1	Updated Study Flow Diagram	Less detailed diagram	Diagram is continually updated as protocol becomes more specifically defined. See additional markers in center column; increased specificity of baseline evals & change of Star Cancellation to Mesulam Unstructured.
35	PR	Section 4: Table 4.3.1	Table inserted	No table	Table was inadvertently dropped from previous submission
36	PR	Section 5: Table 5.2.1	Table inserted	No table	Table was inadvertently dropped from previous submission
37	PR & MOP	PR 9: Table 9.3.2 MOP 2.F, Fig. 2.F.2 re: Enrollment Timeline	Start date adjusted to 8/08	3/08	Grant was not received until August 08; thus timelines have been adjusted accordingly
38	PR & ASAP	ASAP – Orientation, PR 5.1.1	6 tasks – 2 ea.	5-6, 1-2 ea.	Increase specificity/reduce variability in experimental protocol administration

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39	PR & ASAP	ASAP – Orientation, PR 5.1.1,	Partnership Agreement	Collaboration Agreement	Decreased language comprehension requirement
40	PR & ASAP	ASAP MOP, PR 5.2.1	Separate, embargoed, detailed ~ 250 pg. MOP, posted on secure web-site with on-line training materials, print and streaming video examples	Brief 2pg summary + forms, embedded within MOP	Due to conceptual nature of experimental protocol, a detailed, multi-media training package is critical to equipping therapists to carry-out protocol in a standardized & uniform fashion. Need to significantly expand information disseminated to Participant, both verbal & print, in lay-language was met. Embargo necessary to prevent contamination of UCC and preserve scientific integrity.
41	PR& ASAP	ASAP Evaluation, PR 5.1.1	2-hour orientation & eval session	1-2 hour	Increase specificity/reduce variability in experimental protocol administration
42	PR & ASAP	ASAP Standardization, PR 5.2.1	See PR 5.2.1	Less specifically defined	Increase specificity/reduce variability in experimental protocol administration
43	PR & MOP	Screening re: NIHSS (multiple sections) PR 6.3.4	Reduced to items #5, 7, 8 only as they relate to UE function. Complete NIHSS is still administered at Baseline	Complete NIHSS administered during screening & baseline	Reduces burden to participant and clinical site team. Complete assessment is still administered at Baseline
44	PR & MOP	ECS (multiple sections) PR 4.2, 6.2.1.1, 6.3.5	Provides pre-screen of non-modifiable elements as allowed by HIPAA waiver; exclusion criteria updated	N/A	Reduces burden to participant and clinical site team.

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45	PR & MOP	BCS (multiple sections) PR 4.2, 6.2.1.2, 6.3.6	Provides early screen of specific exclusion criteria to allow adequate time to attempt to ameliorate and/or r/o candidate based on unchangeable factors.	No protocol/ order specified. Separate Inc/Exc lists existed with random ordering, i.e. no combining of like items.	Reduces burden to participant and clinical site team.
46	PR & MOP	DCS (multiple sections) PR 4.2, 6.2.1.2, 6.3.7	Moves specific eligibility criteria to late in screening to allow greater time for recovery to occur before determining eligibility;	No protocol/ order specified. Separate Inc/Exc lists existed with random ordering, i.e. no combining of like items.	Reduces burden to participant and clinical site team.
47	PR & MOP	Adverse Events (multiple sections) PR 7, MOP 2.P	Entire section replaced – see documents or reply to DSMB of 12/31/08	See v.3, 8/21/07	Revised to provide better specificity and address concerns of DSMB
48	MOP	2.C Study Org & Responsibilities	Inserted responsibilities for Personnel, Pam Roberts – Program Coordinator for Cedars Sinani	Absent	Inserted description from Proposal

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49	MOP	2.C Study Org & Responsibilities, Consultants	Role of Andrew Butler – TBD	Coordinate informatics portion of the project including: managing personnel, designing an Internet-based server, and data processing for information dissemination across all three study sites.	The study investigators elected to develop a sophisticated, integrated web-based database & information management system from which all study forms, training materials and electronic communications will be generated. This design is beyond the scope of knowledge and expertise of Dr. Butler and his staff, thus this role has been assumed by James Gardner of the ICARE DMAC. Dr. Butler's role and scope of work have not yet been developed and reassigned.
50	MOP	2.C Study Org & Responsibilities, Research Associate	Research Assistant – TBD	Removed former Research Assistant, Bethany Lane	Accuracy - She is no longer on the study
51	MOP	2.C Study Org & Responsibilities, Program Coordinators	Inserted Program Coordinator for Emory – Susan Murphy, replacing Sarah Blanton – Role: TBD	Role designated to Sarah Blanton; role not defined originally	Accuracy – Ms. Murphy replaced Dr. Butler in this role
52	MOP	2.C Study Org & Responsibilities, Program Coordinators	Absent	Removed Program Coordinator, Matt Elrod	Accuracy - He is no longer on the study

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53	MOP	2.C Study Org & Responsibilities, Clinical Site Coordinators	Updated role of Clinical Site Coordinator to parallel the ICARE personnel	Formerly, CSC's had to be licensed clinicians and had dual-responsibilities for not only administration, but also clinical research	Accuracy – it is not required that a Clinical Site Coordinator be licensed or a healthcare provider; 3/7 CSC's do not hold clinical research responsibilities and 2/7 are not licensed clinicians
54	MOP	2.C Study Org & Responsibilities, Clinical Site Coordinators	Updated Personnel	Outdated & incomplete personnel	Accuracy
55	MOP	2.C Study Org & Responsibilities, Clinical Research Evaluators	Updated Personnel	Outdated & incomplete personnel	Accuracy
56	MOP	2.C Study Org & Responsibilities, Clinical Center Coordinators	Updated Personnel & Role	N/A	Accuracy
57	MOP	2.C Study Org & Responsibilities, ASAP Therapists	Updated Personnel	Outdated & incomplete personnel	Accuracy
58	MOP	2.C Study Org & Responsibilities, UCC Therapists	Updated Personnel	Outdated & incomplete personnel	Accuracy
59	MOP	2.C Study Org & Responsibilities, DEUCC Therapists	Updated Personnel	Outdated & incomplete personnel	Accuracy

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60	MOP	2.C Study Org & Responsibilities, FAS Rater Panel	Updated Personnel & Role	Outdated & incomplete personnel	Accuracy
61	MOP	Figure 2.C.2	Updated CCRC	Centinela Freeman	Accuracy
62	MOP	2.C.2.3	Updated CCRC	Centinela Freeman	Accuracy
63	MOP	2.C.5	Updated Personnel	Outdated & incomplete personnel	Accuracy
64	MOP	2.C.6	Updated Personnel	Outdated & incomplete personnel	Accuracy
65	MOP	2.C.9	Updated Personnel	Outdated & incomplete personnel	Accuracy
66	MOP	2.D	Updated to reflect training that has already occurred, availability of training materials on the ICARE web-site, and training that is still underway.	Anticipatory of training	Accuracy
67	MOP	2.E	Updated to reflect current and future anticipated practices; added quarterly safety report to DSMB, as per its request.	Outdated & incomplete personnel	Accuracy
68	MOP	2.F	Updated to reflect current timeline	Prior timeline	Date of Grant Award Changed – Accuracy
69	MOP	2.G	Updated to reflect current procedure	See MOP of 8/21/07	Accuracy

Manuals Key: PR = Protocol; MOP = Manual of Procedure; ASAP = ASAP Manual of Procedure; SAP = Statistical Analysis Plan Manual of Procedure; CRF = Clinical Resource Forms Screening Phases: ECS = Express Chart Screen; BCS = Brief Clinical Screen; DCS = Detailed Clinical Screen; MSB = Medical Screen at Baseline; FCE = Baseline Evaluation, Final Check for Exclusion

ICARE MANUALS OF PROCEDURE – REVISIONS TABLE					
#	MANUAL CHANGED	SECTIONS IMPACTED	CURRENT/REVISED PROCEDURE	PRIOR PROCEDURE	RATIONALE
70.	MOP	2.H	Updated to reflect current procedures and screening tools	See MOP of 8/21/07	Accuracy, also added the specific screening tools, a they were not present in the previous version
71.	MOP	2.I	Updated to incorporate changes in screening procedure & eligibility determination; change from Star Cancellation to Mesulam & changes in evaluations. Updated sample IFC's accordingly	See MOP of 8/21/07	Accuracy
72.	MOP	2.J	Updated to incorporate current procedures		Accuracy
73.	MOP	2.M	Updated to include current evaluations & order, change to web-generated forms and web-based training materials	See MOP of 8/21/07	Accuracy
74.	MOP	2.P	Protocol implemented in Dec 08 in response to DSMB feedback	See MOP of 8/21/07	Accuracy
75.	MOP	2.Q	Updated with new info from SAP	See MOP of 8/21/07	Accuracy
76.	MOP	2.R	Updated to report fundamental change to database generated forms	See MOP of 8/21/07	Accuracy
77.	MOP	2.S	Updated to report fundamental change to database generated forms	See MOP of 8/21/07	Accuracy
78.	MOP	2.T	Updated to incorporate SAP	See MOP of 8/21/07	Accuracy

Manuals Key: PR = Protocol; MOP = Manual of Procedure; ASAP = ASAP Manual of Procedure; SAP = Statistical Analysis Plan Manual of Procedure; CRF = Clinical Resource Forms Screening Phases: ECS = Express Chart Screen; BCS = Brief Clinical Screen; DCS = Detailed Clinical Screen; MSB = Medical Screen at Baseline; FCE = Baseline Evaluation, Final Check for Exclusion

ICARE MANUALS OF PROCEDURE – REVISIONS TABLE					
#	MANUAL CHANGED	SECTIONS IMPACTED	CURRENT/REVISED PROCEDURE	PRIOR PROCEDURE	RATIONALE
79	MOP	2.U	Updated to include current evaluations & order, change to web-generated forms and web-based training materials	See MOP of 8/21/07	Accuracy

Manuals Key: PR = Protocol; MOP = Manual of Procedure; ASAP = ASAP Manual of Procedure; SAP = Statistical Analysis Plan Manual of Procedure; CRF = Clinical Resource Forms Screening Phases: ECS = Express Chart Screen; BCS = Brief Clinical Screen; DCS = Detailed Clinical Screen; MSB = Medical Screen at Baseline; FCE = Baseline Evaluation, Final Check for Exclusion

INTERDISCIPLINARY COMPREHENSIVE ARM REHABILITATION EVALUATION (ICARE):

STATISTICAL ANALYSIS PLAN (SAP)

Original

May 15, 2009

(Excerpted verbatim from Data Management Plan, which also included study summary, structure of data management and analysis center, randomization and blinding, sample size estimates, interim data analysis, data management and reporting, including adverse events, maintenance of public website, and technical specifications)

9. DATA ANALYSIS

We begin by characterizing the study sample using descriptive statistics to demonstrate the distribution of demographics and baseline characteristics. This will include mean, median, standard deviation and range for continuous variables and frequency for categorical variables. The distribution will be produced for the overall sample, and again for each randomized group, separately. Details are provided below of the comprehensive statistical data analysis plan for each hypothesis. For all analyses, assumptions required for the data distribution (e.g., normal distribution) will be checked. Any transformations of data or alternative methods necessary to analyze the data will be determined by examining the structure of the data. All analyses will be performed in accord with the intent-to-treat principle (ITT, i.e., group status will be determined by randomization at baseline). For subjects who miss evaluation visits or dropouts, therefore with missing data, every effort will be made to collect the primary and some of the secondary outcomes. Our weekly data quality report, periodic investigator meetings will identify these problems early and appropriate actions will be taken to minimize the missing data prior to trial end. For ITT analyses, all randomized subjects will be included no matter what treatment received. For subjects who miss subsequent visits after baseline, their subsequent visit data will be imputed based on their baseline characteristics and data observed from subjects who had follow-up visits. For subjects who had at least one follow-up evaluation but miss some of the follow-up visits, their missing visit data will be computed incorporating both baseline and follow-up data collected. We will use multiple imputation to handle the missing data, i.e., replace each missing value with a set of plausible values that represent the uncertainty about the right value. The multiple imputed data sets are then analyzed by using standard procedures for

complete data and the results are combined from these analyses. This approach is valid when data that are missing is at random (MAR), i.e., no new information can be gained in the missing data given the data that we measured already. Although the MAR assumption cannot be verified with the data and it can be questionable in some situations, the assumption becomes more plausible as more variables are included in the imputation model. SAS PROC MI will be used to estimate the missing data and PROC MIANALYZE will be used to combine the results from the multiple imputations. Pattern of missing data will be evaluated and appropriate detail imputation approach will be decided. For example, for monotone missing pattern, i.e., once a subject misses the visit, no subsequent follow-up data are available (e.g, dropouts), regression method or the predictive mean matching method can be used. For arbitrary missing pattern, the Markov Chain Monte Carlo (MCMC) simulation can be used to estimate the missing data. To assess the impact of missing data on our trial results, we will also perform secondary complete case analyses. Baseline characteristics between subjects who do and do not complete the trial will be compared. Any differences in results between ITT estimating missing data and ITT complete case analyses will be interpreted carefully and its impact on generalization of the trial results. In addition, dropouts between randomized groups will be compared to assess any possibility of differential dropouts that might relate to treatment. We have incorporated a 25% dropout rate in our sample size estimation; this is on the high end of estimations based on our previous experience. Thus, we expect to have the power as we have planned. To evaluate impact of treatment non-compliance on trial results, if subject compliance to the treatment protocol assigned is low, secondary analyses will also be conducted based on actual treatment and dose received. Results from this analysis will be compared to the ITT analysis and any discrepancy will be reported and interpreted with caution. We will perform a sensitivity analysis using other non-standard methods that have been proposed in the statistical literature dealing with protocol non-compliance. All methods have underlying assumptions that are not testable, thus, sensitivity analysis is appropriate. Consistency of results from all approaches will provide assurance of the trial results. Any discrepancies will be investigated further.

9.1 SPECIFIC AIM 1-ANALYTIC PLAN

This aim compares ASAP to DEUCC group and is the pre-planned primary aim with the primary outcome defined as change in time score from the WMFT and the secondary outcome as the success rate from SIS hand function. The sample size is based on this aim with a type I error of 0.05, thus, a p-value of less than 0.05 will be used to declare significance. Baseline characteristics between ASAP and DEUCC groups will be compared first to assess whether randomization has achieved balance at baseline. Continuous variables will be compared using two-group t-test for normally distributed variables to test for mean differences and Wilcoxon rank sum test will be used for non-normally distributed variables to test for median differences. Chi-square or Fisher's exact test will be used for categorical variables to test for frequency differences. Characteristics that differ

at baseline will be included as covariates in analyzing the primary and secondary outcomes. For primary outcome change in time score from WMFT at 1yr, a two-group t-test will be used to compare the mean change in log-transformed WMFT time score and analysis of covariance (ANCOVA) will be used to adjust for baseline variables that differ between groups and the stratified variables (center, initial motor impairment, time from onset to randomization). Adjusted least-square means and the associated 95% confidence interval will be presented as well as p-value. For the secondary outcome success rate in SIS hand function, success rate will be calculated as the percent of subjects in the ASAP and DEUCC groups that achieved a 25 point increase in normalized SIS hand function at 1 yr post treatment compared to baseline. The success rates in SIS hand function between groups will then be compared by logistic regression. The dependent variable is success (yes or no) and the independent variables are treatment group and covariates are baseline variables that differ between groups and the stratified variables. Adjusted rate ratio and the associated 95% confidence interval will be presented as well as p-value. Since there is no prior data or biological evidence suggesting that ASAP will have a differential effect on one subgroup compared to the other in the population we target, we do not plan to test for an interaction between treatment and any of the covariates in the main analysis. However, we will explore plausible interactions (see 9.5.3) through exploratory data analysis to generate hypotheses for future studies. For other secondary outcomes including WMFT functional ability score (FAS), strength, and full SIS, changes in normalized self-reported scores in strength, ADL/IADL, mobility, communication, emotion, memory and thinking, and participation at 1-yr post from baseline will be compared between ASAP and DEUCC groups using analysis of covariance. In addition, a composite physical domain, which includes strength, hand function, ADL/IADL, and mobility, will be created and compared in a similar way.

9.2 SPECIFIC AIM 2-ANALYTIC PLAN

This is the secondary aim. Aim 2A compares ASAP to UCC and Aim 2B compares DEUCC to UCC to assess a pure dose effect of usual therapy. The analytic approach is the same as that described for the primary aim (Sec 9.5.1) except ASAP will be compared to UCC under Aim 2A and DEUCC will be compared to UCC under Aim 2B. Briefly, outcomes include WMFT time score and success rate for SIS hand domain and changes in full SIS domains at 1-yr post randomization from baseline. Logistic regression will be used to compare the success rate and ANCOVA will be used to compare changes in full SIS domain and WMFT between groups. Any baseline measures that differ at baseline and stratified baseline variables will be included as covariates.

9.3 OTHER SECONDARY AND EXPLORATORY DATA ANALYSIS PLANS

For other secondary measures including those outlined in 5.8.3 and 5.8.4, we will take a similar approach as described above to assess differences between

groups. In general, for dichotomous outcomes, logistic regression, and for continuous outcomes, ANCOVA will be used. Unbalanced baseline covariates and stratified variables will be included as covariates. For exploratory data analysis, possible interactions between treatment and baseline variables, such as high or low motor impairment groups, time from stroke onset to randomization, stroke types (ischemic vs. hemorrhagic), age and gender groups will be tested. If significant, the nature of the interaction will be further characterized by performing subgroup analyses. Baseline continuous variables will be categorized in order to allow a clinically meaningful presentation/interpretation. Cut-points will be defined by the overall distribution across the three groups. The results of these exploratory analyses will be used only to generate hypotheses for designing future confirmative studies. In addition, we will include immediate post treatment and 6-month follow-up analysis to assess overall time trend differences between groups. The outcome data will be plotted or graphed against time (baseline, immediate post intervention and 1-yr post randomization) to visually examine any patterns of change. These longitudinal data will be modeled using mixed-effects model to quantify and test for the overall treatment effect by testing for interaction between group and time and test for the pattern of treatment effect difference at different evaluation points by testing for a three way interaction among group, time and evaluation point. Intercept will be specified as a random effect. A significant three-way interaction suggests that treatment has different effects on the outcome during the trial. For example, treatment effect did not start until immediate post-treatment, or treatment effect plateaus after 6-month post treatment, etc. Once such different patterns are identified, further stratified analyses will be conducted to evaluate the nature of any treatment group differences. All analyses will consider appropriate baseline difference adjustments.

Finally, and corresponding to the International Classification for Disability and Functioning model⁹¹, with linkages between body function/structure, activity, and participation, we will examine the relationship between changes in upper extremity activity (WMFT) and self-reported hand function (SIS) using our primary and secondary outcomes. These exploratory analyses will compare the change in WMFT performance and several subdomains of the SIS including hand function, composite physical function, and social participation. To this end, path analysis methods will be implemented.

SAS (SAS Institute Inc, Cary, NC) will be the primary software used for all statistical analysis. We will use SAS PROC LOGISTIC for logistic regression, SAS PROC GLM for ANCOVA, and SAS PROC MIXED and PROC NL MIXED for repeated measures longitudinal data analysis.

9.4 MULTIPLE COMPARISON ISSUE AND RESULTS INTERPRETATION

This trial addresses two different questions separated by primary aim and secondary aim: 1) is ASAP superior to DEUCC (primary aim), and 2) is ASAP

superior to UCC, and is DEUCC superior to UCC (secondary aim). We propose to adopt type I error of 0.05 for each of the two questions. The first question (primary aim) has one comparison, therefore, no multiple comparison adjustment needed. The secondary aim has two comparisons (ASAP vs. UCC, DEUCC vs. UCC). We propose to use Bonferroni method to control the type I error for the second questions, that is, a p-value of 0.025 will be used to declare significance for the comparison between ASAP and UCC, between DEUCC and UCC. When reporting the trial result, we will make it clear which is the primary aim and which is the secondary aim.

The following specifies interpretation of data given each possible outcome scenario: First, if our primary aim is supported, the findings of ICARE could change current practice patterns during post-acute outpatient therapy for those with mild to moderate baseline impairments, ASAP should be recommended for practice. The results from the secondary aim will provide additional useful information. Second, if our primary aim is not supported, the results from the secondary aim would be of interest. If both ASAP and DEUCC superior to UCC, it suggests that doses alone matters. The findings of ICARE could establish recommendations for the number of outpatient visits necessary to achieve clinically meaningful outcomes and for which no guidelines currently exist. If none of the ASAP or DEUCC superior to UCC, then current practice of usual and customary care should continue. If only one of the ASAP or DEUCC (but not both) superior to UCC, the nature of the difference will be examined to make relevant interpretation. In any case, we will clearly spell the primary aim and secondary aim when reporting ICARE results.

INTERDISCIPLINARY COMPREHENSIVE ARM REHABILITATION EVALUATION (ICARE):

STATISTICAL ANALYSIS PLAN (SAP)

Final

Sept 15, 2014

(Excerpted verbatim from final Data Safety Monitoring Report section 4.)

4.1 Statistical Analysis Plan

4.1.1 Data manipulation (coding, missing data and imputation)

Data coding: In preparation for data analyses, summary scores for outcomes were computed. For continuous outcomes, normality was assessed, and potential outliers were identified to confirm correct data entry and provide information about possible leverage points. Transformations of continuous data were made if required to meet model assumptions. If no sufficient transformation was possible, non-parametric methods were used to answer research questions. Table 4.1.1 summarizes the outcomes by ICR domain, any data manipulation performed, and ranges of responses to aid in interpretation of results.

Missing Data & Imputation: When computing summary scores, our general rule for excluding a participant's summary score was if $\geq 20\%$ of the components of the score were missing. Due to the structure of some of the scales, more missing items might be allowed (up to 50%). For scales that included weighting, no missing items were allowed. Table 4.2.2.A summarizes the percent of missing summary scores for outcomes for any reason.

Patterns of missing data were summarized (Table 4.2.2.B) and analyzed to determine if they were related to the outcome (not missing at random (NMAR)), related to a covariate and thus imputable (missing at random (MAR)), or unrelated to any study related factors (missing completely at random (MCAR)). For participants with 12-month observations missing, data was imputed from on their baseline characteristics (age, gender, ethnicity, race, type and location of stroke, side of hemiparesis, and number of days from stroke to randomization) and any follow-up visits. We used multiple imputation (SAS PROC MI) to handle the missing data, i.e., replace each missing value with a set of plausible values that represent the uncertainty about the right value. The multiple imputed data sets were then analyzed by using standard procedures for complete data and the results are combined from these analyses (SAS MIANALYZE). Because the pattern of missing data in our sample was non-monotone, we utilized the Markov Chain Monte Carlo (MCMC) imputation methods using the full-data set available. This approach is valid when data that are missing is at random (MAR). i.e., no new information can be gained in the missing data given the data that we measured already. To assess the impact of missing data on our trial results, we will also perform secondary complete case analyses.

Baseline characteristics of participants who did and did not complete the trial were compared to inform on generalizability of the trial results. In addition, dropouts across randomized groups were compared to assess any possibility of differential dropouts that might relate to treatment. We estimated *a priori* 17-25% attrition at 12-months. Evaluable data at 12-months was 84% for WMFT, thus we should be sufficiently powered for all analyses.

4.1.2 Descriptive statistics

Section 3 of the Final report characterized the study sample using descriptive statistics to demonstrate the distribution of demographics and baseline characteristics (Tables 3.3.1 A/B). We characterized the continuous variables as mean, median, standard deviation and range for continuous outcomes and N (%) for categorical outcomes. Comparison of outcomes at baseline across groups and by stratification factors were made using ANOVA for continuous outcomes or χ^2 tests for categorical outcomes. A comparison of just ASAP and DEUCC (our primary aim) was also performed, however, there were no significant differences in the baseline outcomes. Any baseline characteristics that differed across groups were used as covariates in ITT models. Bivariate associations of outcomes across time were performed using Spearman correlations, in order to reduce the influence of outliers. Additionally, associations with stratification factors were made as described above for group.

4.1.3 Intent-to-treat analyses

Primary Aim: ASAP vs DEUCC. For ITT analyses, all randomized participants will be included regardless of treatment received. Comparison of ASAP vs DEUCC was the *priori* primary aim of ICARE, while other group comparisons were secondary. The primary outcome was improvement in WMFT time score across 12 months, and the secondary outcome was success rate as determined by the SIS hand function.

For the primary 2-group comparison of ASAP to DEUCC, mean change in log-transformed WMFT time score will be tested using a 2-group analysis of covariance (ANCOVA) adjusting for baseline values and the stratification variables (site, initial motor impairment (Fugl-Meyer), time from onset to randomization (<60 vs 60+)). Adjusted marginal means were computed along with estimate of effect size (Cohen's D). Residuals were examined to determine if assumptions were met, and whether there were outliers acting as leverage points. If outliers were detected, models were run without the outliers and compared with the complete data to examine the potential influence of those points.

For the secondary outcome success rate in SIS hand function, success rate was calculated as the percent of participants in the ASAP and DEUCC groups that achieved a 25 point increase in normalized SIS hand function at 1 yr post treatment compared to baseline. The success rates in SIS hand function between groups was then compared by logistic regression, adjusting for covariates as described above.

Secondary Aims and outcomes. Aim 2A compared ASAP to UCC and Aim 2B compared DEUCC to UCC to assess a pure dose effect of usual therapy. The analytic approach was the same as that described for the primary aim. For other secondary outcomes, including WMFT functional ability score (FAS), strength, and SIS hand function, ADL/IADL and SIS 16 was compared between ASAP and DEUCC groups using analysis of covariance or logistic regression models as described above. For all analyses, assumptions required for the data distribution (e.g., normal distribution) will be examined and adjustments made as required so that the models are deemed valid.

Multiple Comparison issue and results interpretation. This trial addressed two different questions separated by primary aim and secondary aim: 1) was ASAP superior to DEUCC (primary aim), and 2) was ASAP superior to UCC, and was DEUCC superior to UCC (secondary aim). We adopted type I error of 0.05 for each of the two questions. The first question (primary aim) had one comparison; therefore, no multiple comparison adjustment was needed. The secondary aim had two comparisons (ASAP vs. UCC, DEUCC vs. UCC), thus we used Bonferroni's method to control the type I error so a p-value of 0.025 would be used to declare significance for the comparison between ASAP and UCC, between DEUCC and UCC. For all analyses, any $p < 0.10$ was reviewed.

4.1.4 Exploratory analyses

In addition to the statistical analyses specified *a priori*, we also performed exploratory statistical analyses related to the primary aims. **Consistency of results across approaches provides assurance of the trial**

results, whereas inconsistencies provide opportunities to discover subtleties in the data that is not evident in the ITT analyses.

Severity and Time since Onset Interaction Models. In addition to the models of main effects of group, adjusted for site, severity, and time since stroke onset, we explored 2- and 3-way interactions of group with severity and time since onset. These were an extension of the ITT models described above. Because we were not powered to detect interaction effects, group interactions with $p \leq 0.10$ are reported.

Treatment type and dose. To evaluate impact of treatment non-compliance on trial results, secondary analyses will examine the influence of type of treatment (ASAP or UCC) and dose of treatment (hours) received, and how these might differ from ITT which combine these analyses. For these analyses, instead of treatment group, the main factors were hours of the two types of treatment: ASAP and UCC. These analyses only included participants with some treatment ($N = 325$). There were 36 participants (10%) who received no treatment: 9 were assigned to ASAP, 3 were assigned to DEUCC, and 24 were assigned to UCC. Additionally, there were 19 (16%) ASAP participants who received UCC therapy in addition to ASAP (see Tables 3.2.9.A-C).

Intervention phase vs follow-up phase. Longitudinal mixed effect (LME) models were utilized to model change in outcomes that occurred during the treatment phase (baseline to post-intervention) and the follow up phase (6-12 months). This LME modeling allows for the correction for missing data using the model of best fit, and allows for the adjustment of possible bias due to differential adherence between groups. To examine these two different segments, a spline model was created, using months as the time variable so that beta coefficients can be interpreted as rate of change per month and can be directly compared between treatment and follow-up phases. A heterogeneous first-order autoregressive covariance structure was used, which specifies correlated residual errors within a participant, but no correlation across individuals and allows different variances in outcome across time. Models proceeded as such: (1) Time models, (2) Group effects, (3) Adjustment for *a priori* covariates, and (4) addition of adherence (number of hours of treatment) received was included in these models. The time models included 2-steps: first a linear model was created to determine if there was change across 12-months. Then the spline model was created to see how much of the change at 12 months occurred during the intervention phase vs follow up. (For MAL-28, which was not measured at baseline, only linear models were used.) Group effects were tested as main effects and interactions. If the interaction effects had $p > .10$, then a main effects model only was used. All groups were modeled simultaneously with ASAP as the reference group. Then the adjusted group effects were modeled, first accounting for *a priori* covariates (severity at onset, time since stroke, and site), and then for adherence (total hours of treatment).

SAS version 9.3 (SAS Institute Inc, Cary, NC) will be the primary software used for all statistical analysis. We will use SAS PROC LOGISTIC for logistic regression, SAS PROC GLM for ANCOVA, and SAS PROC MIXED and PROC NLMIXED for repeated measures longitudinal data analysis. Additionally, analyses will be performed with SPSS (v.21).